Cell Fate

Судьба клетки: деление, дифференцировка, старение, апоптоз

с/к Межклеточная коммуникация

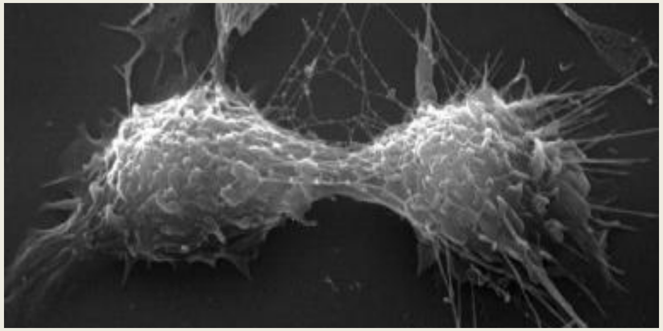
Лекция 6

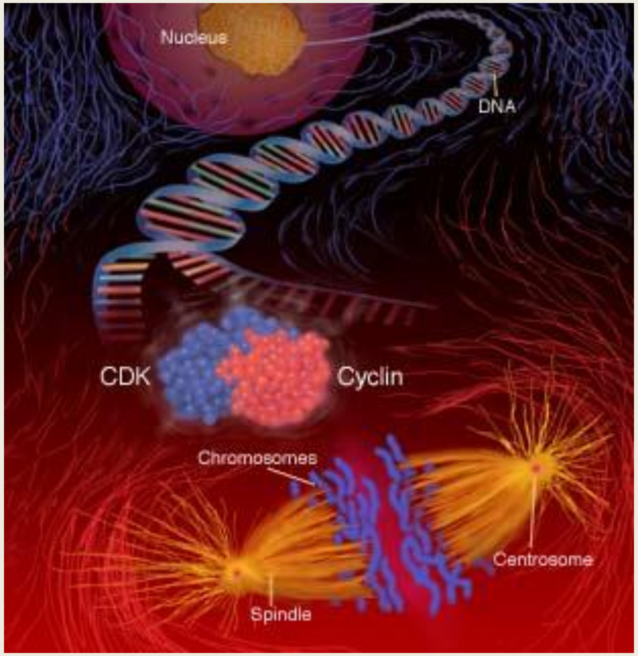
Cellular homeostasis

Proliferation ↔ Arrest

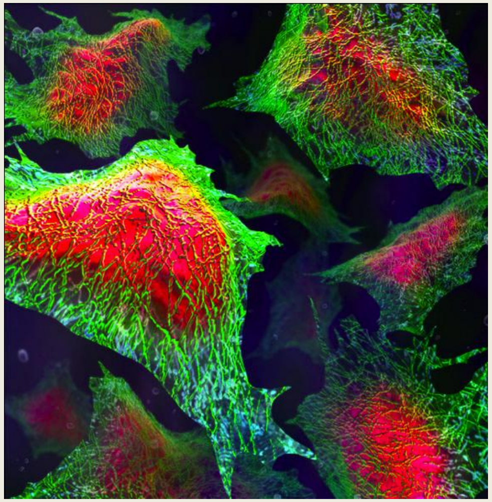
Survival ↔ Apoptosis

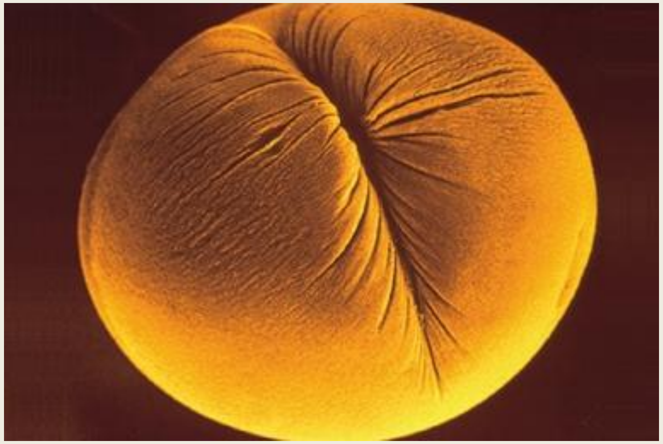
Undifferentiated ↔ Differentiated

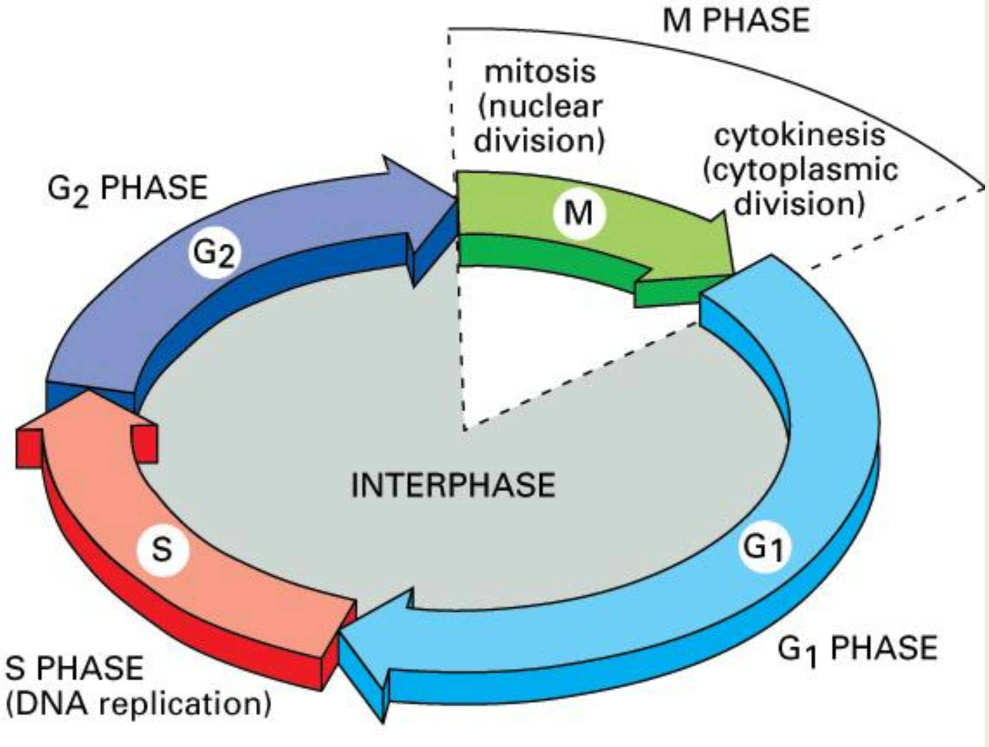


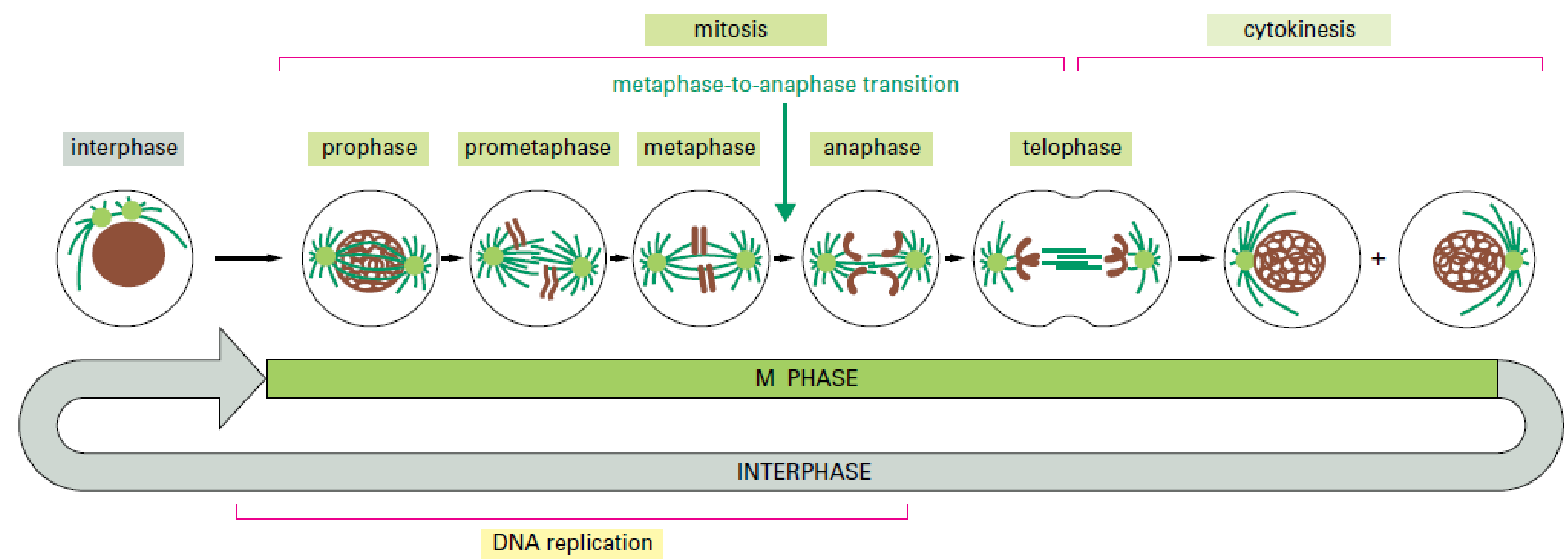


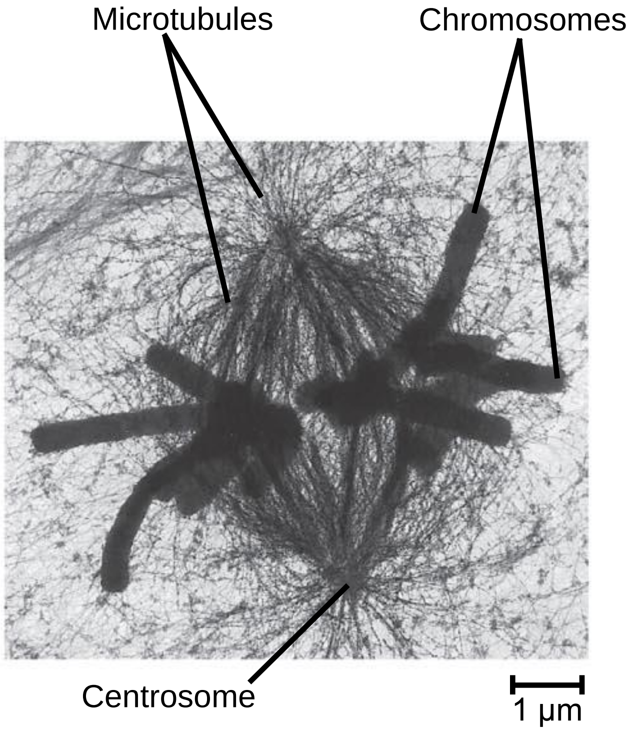
Eukaryotic Cell Division

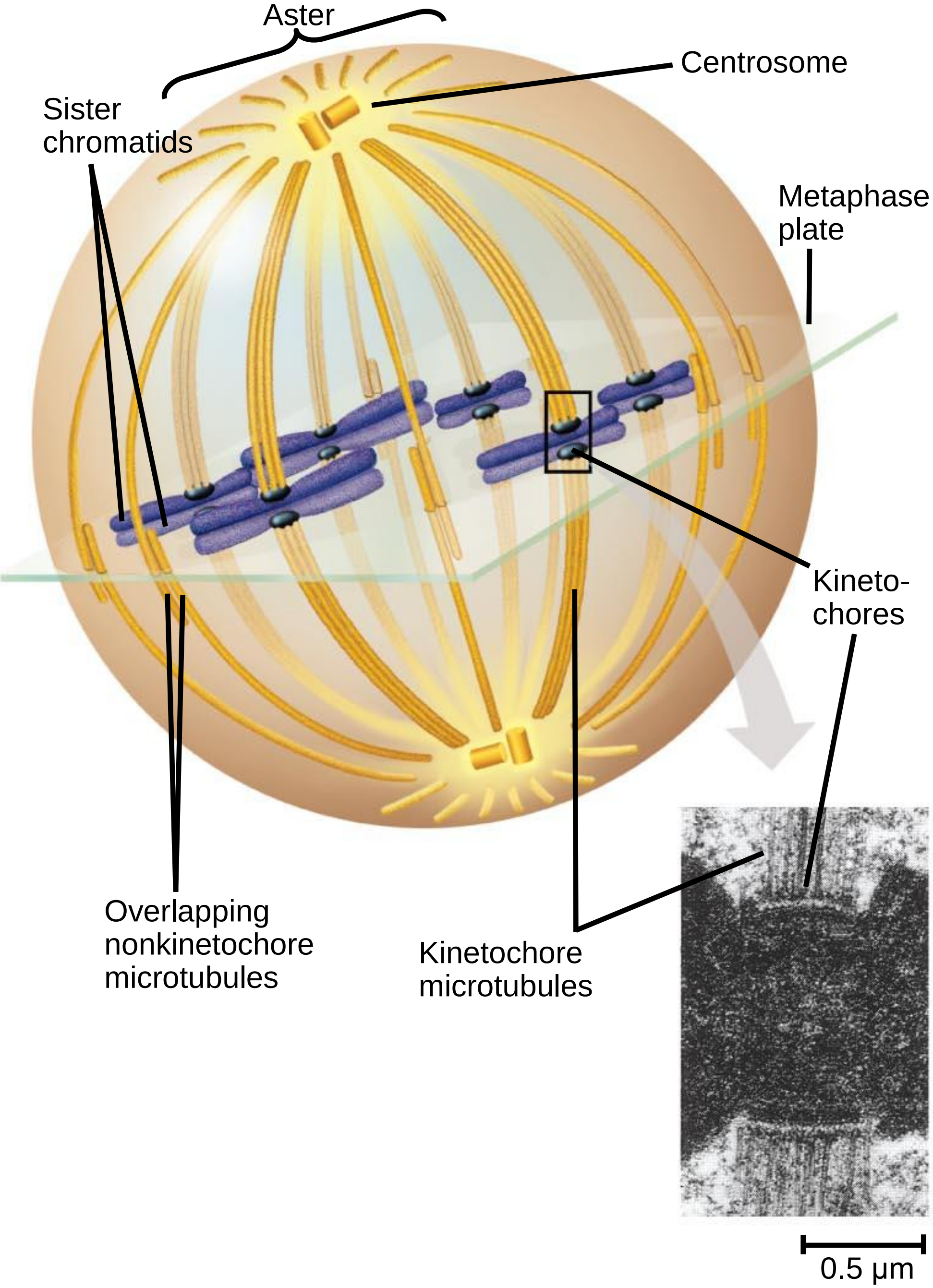





M PHASE
mitosis (nuclear division)
cytokinesis (cytoplasmic division)
G_2 PHASE
G_2
M
INTERPHASE
S
G_1
S PHASE (DNA replication)
G_1 PHASE


mitosis
cytokinesis
metaphase-to-anaphase transition
interphase
prophase
prometaphase
metaphase
anaphase
telophase
+
M PHASE
INTERPHASE
DNA replication





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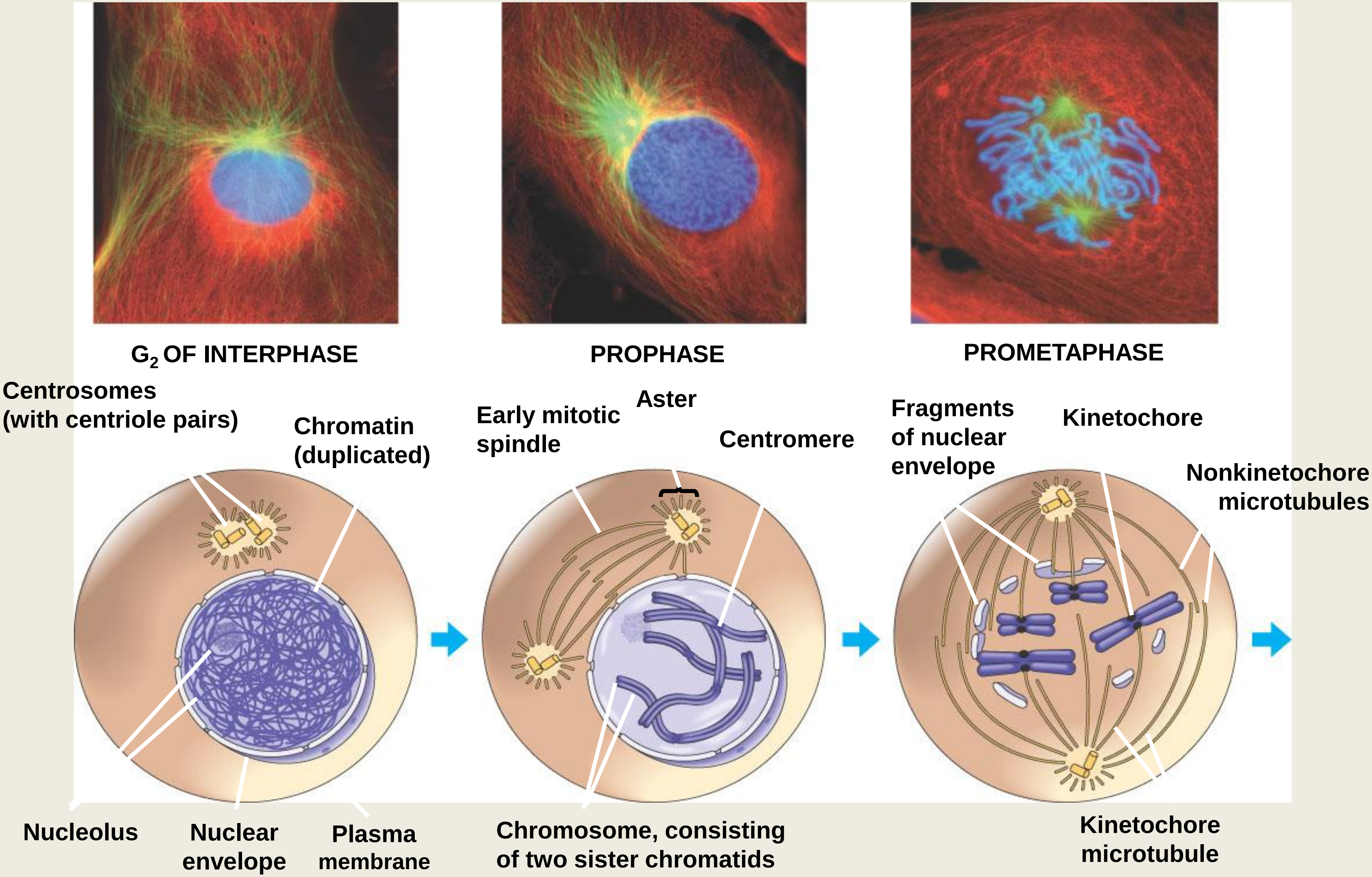
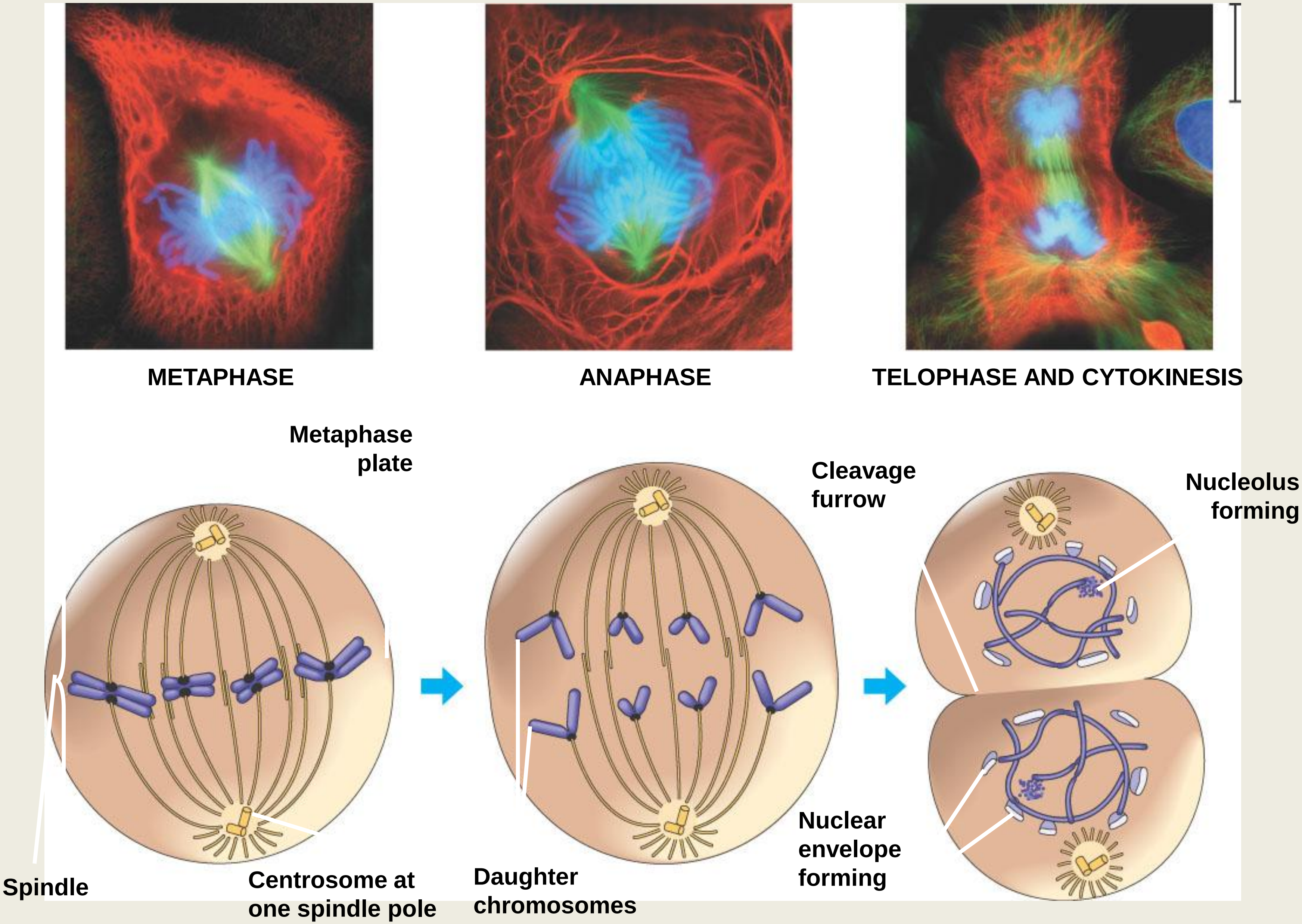


G_2 OF INTERPHASE

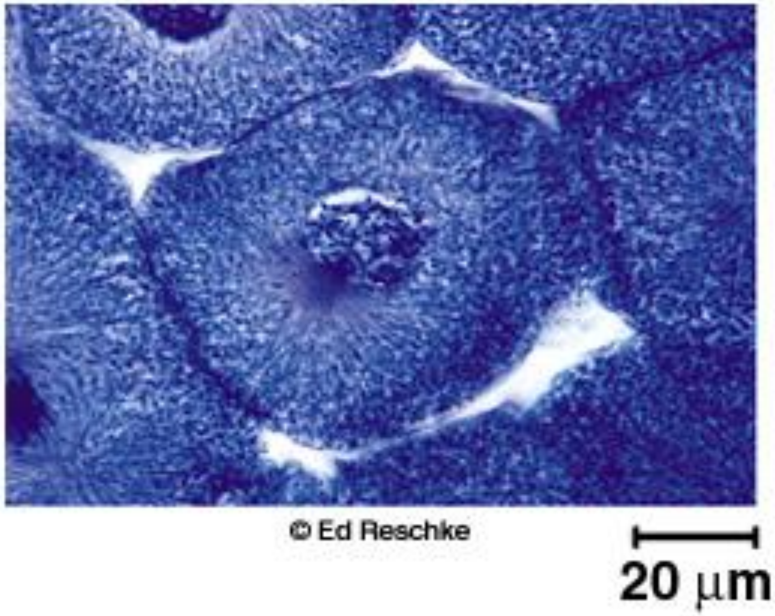
PROPHASE

PROMETAPHASE

Centrosomes (with centriole pairs)
Chromatin (duplicated)
Nucleolus
Nuclear envelope
Plasma membrane
Early mitotic spindle
Aster
Centromere
Chromosome, consisting of two sister chromatids
Fragments of nuclear envelope
Kinetochore
Nonkinetochore microtubules
Kinetochore microtubule


METAPHASE
ANAPHASE
TELOPHASE AND CYTOKINESIS
Metaphase plate
Cleavage furrow
Nucleolus forming
Spindle
Centrosome at one spindle pole
Daughter chromosomes
Nuclear envelope forming

Nondividing cell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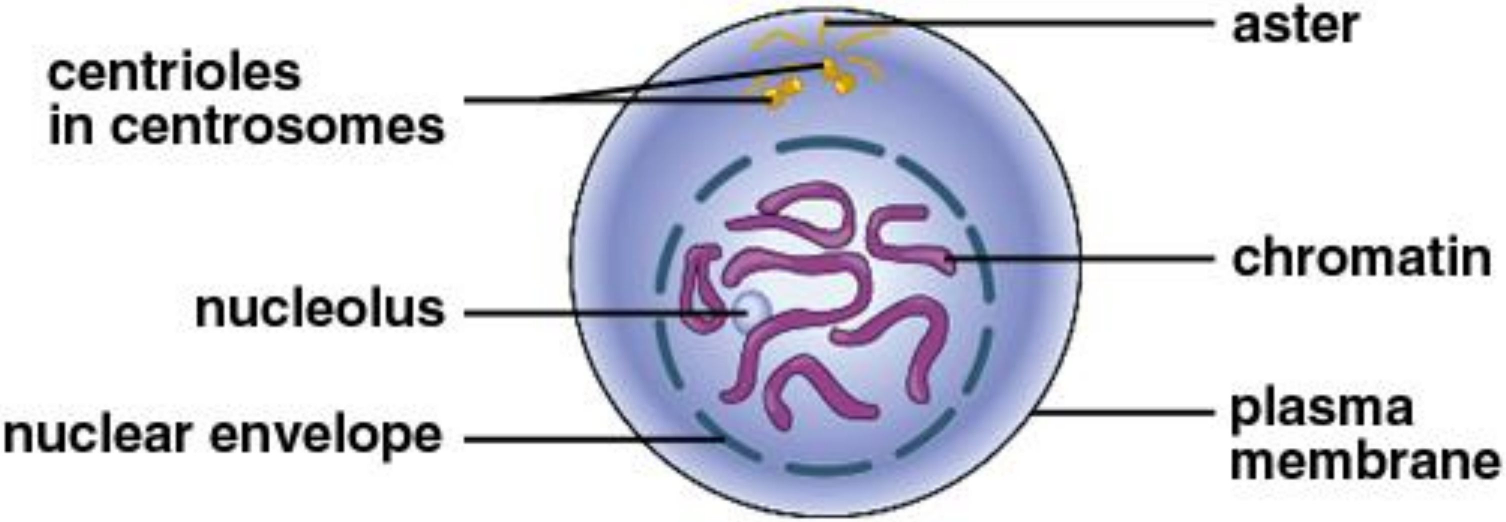
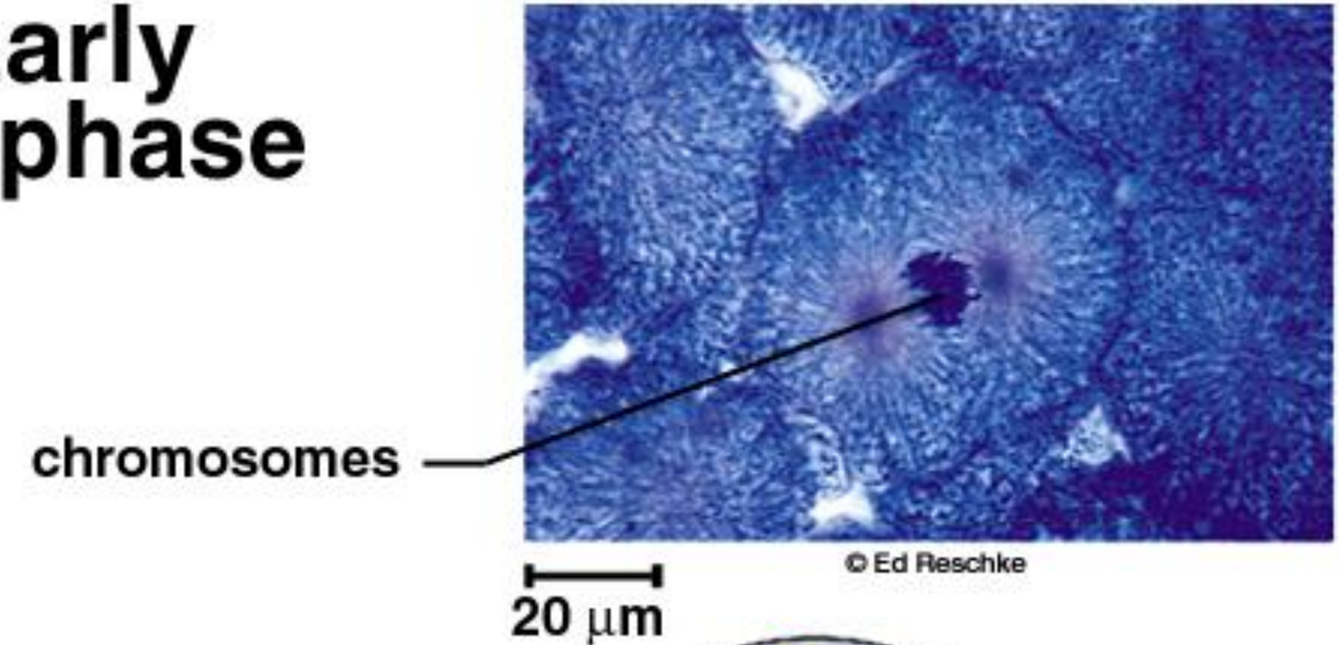


Nondividing Cell

Chromatin is condensing into chromosomes and centrosomes have duplicated in preparation for mitosis.

Early prophase



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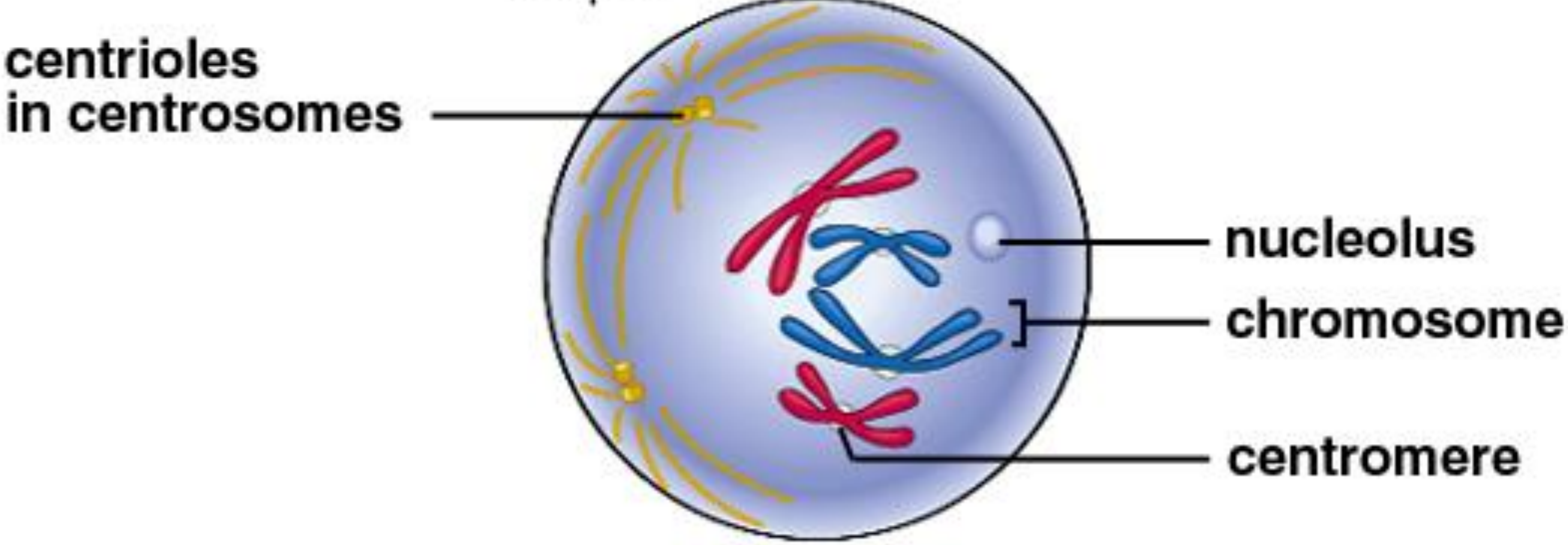
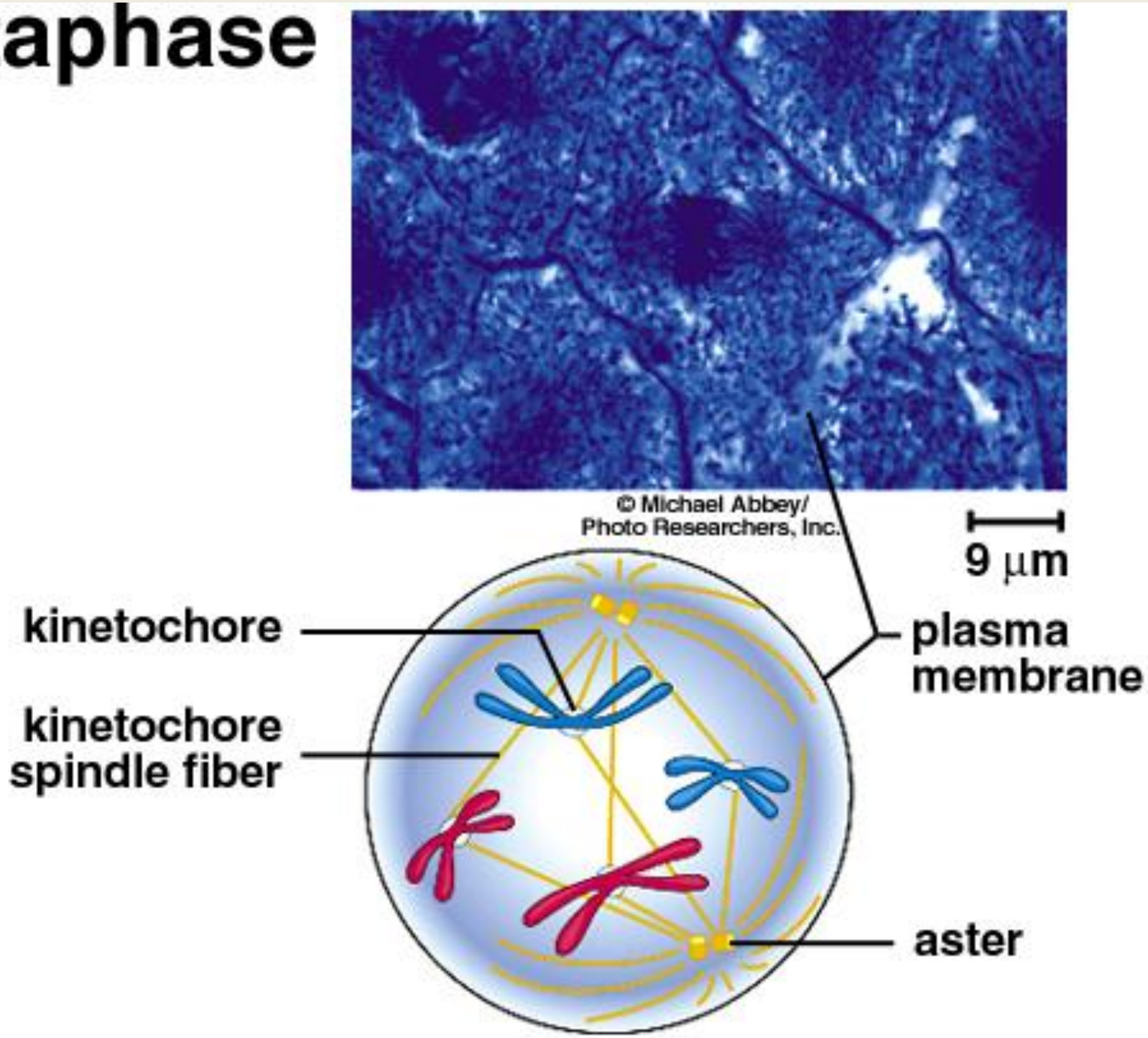


Prophase

Chromosomes are duplicated. Centrosomes begin moving apart; nuclear envelope is fragmenting and nucleolus will disappear.

Prometaphase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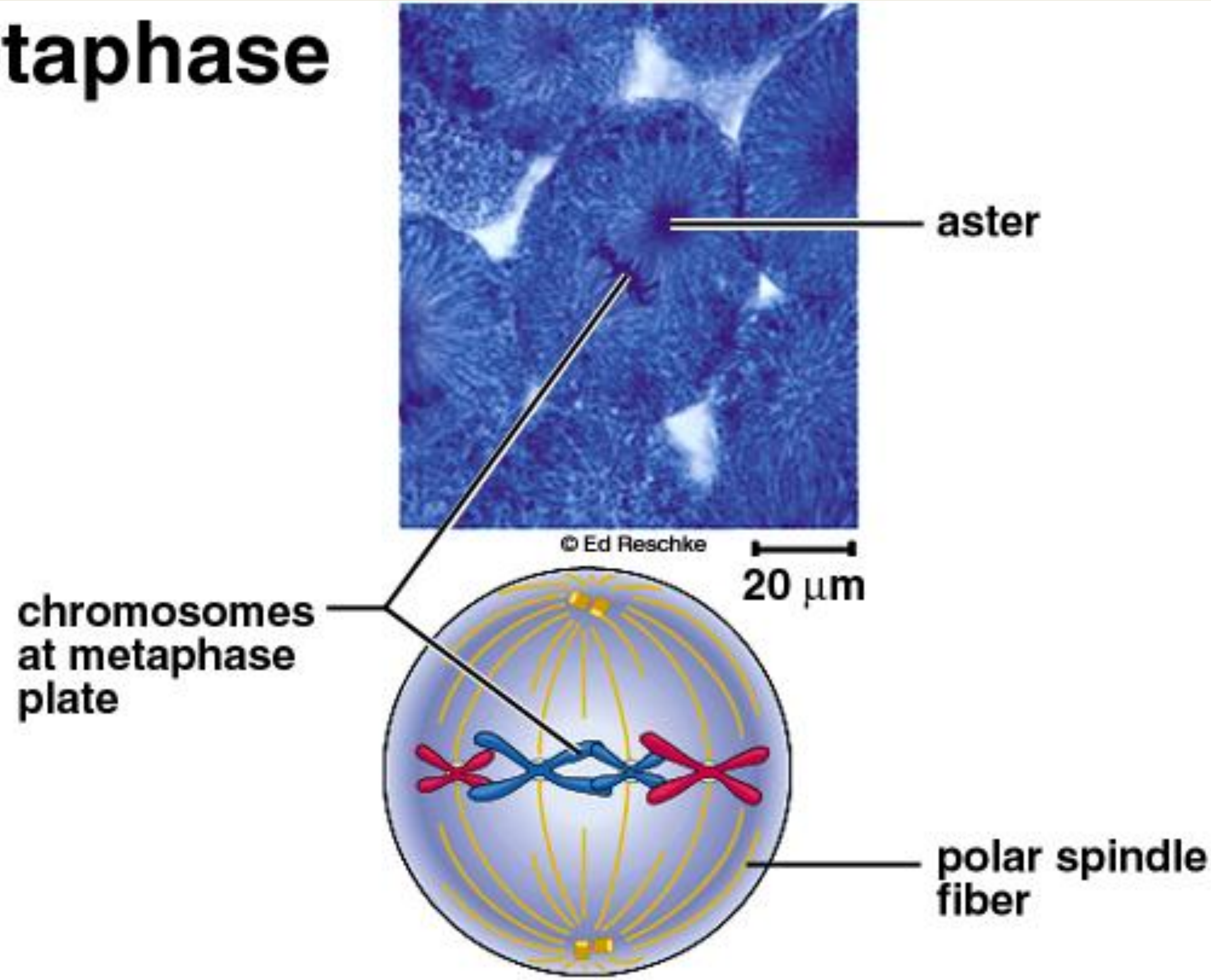
Prometaphase

Spindle is in process of forming, and kinetochores of chromosomes are attaching to kinetochore spindle fibers.

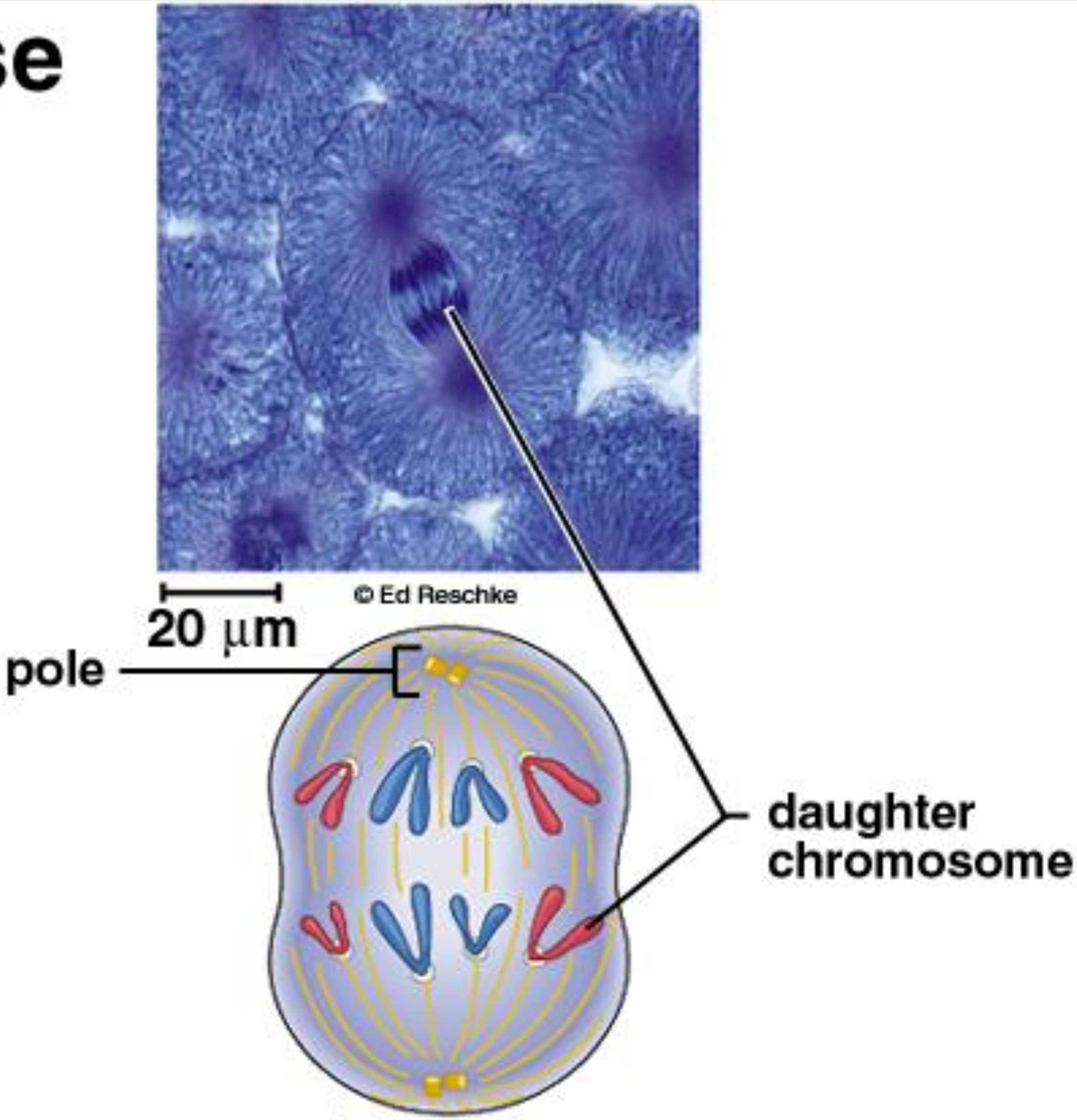
Metaphase



Metaphase

Chromosomes (each consisting of two sister chromatids) are at the metaphase plate (center of fully formed spindle).

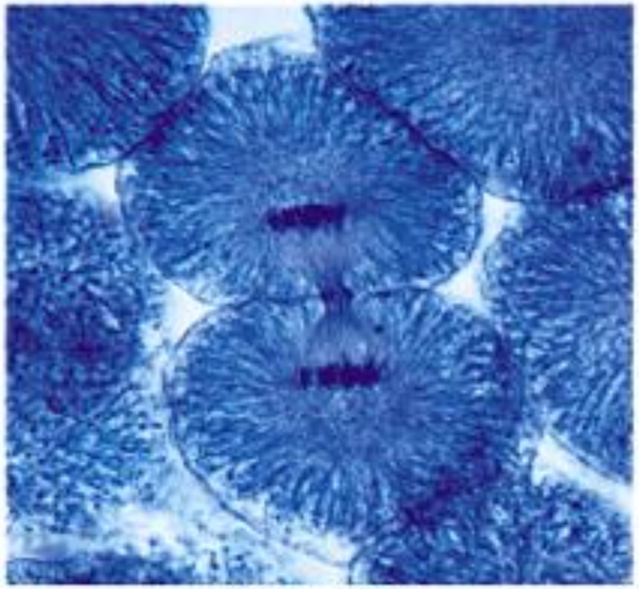
Anaphase



Anaphase

Daughter chromosomes (each consisting of one chromatid) are moving toward the poles of the spindle.

Telophase



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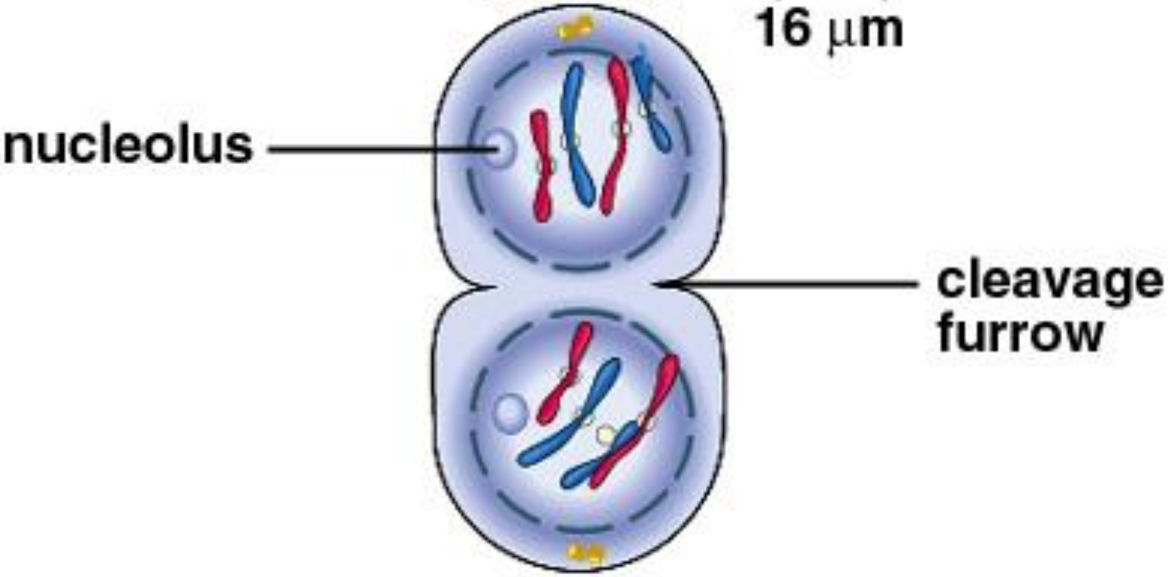
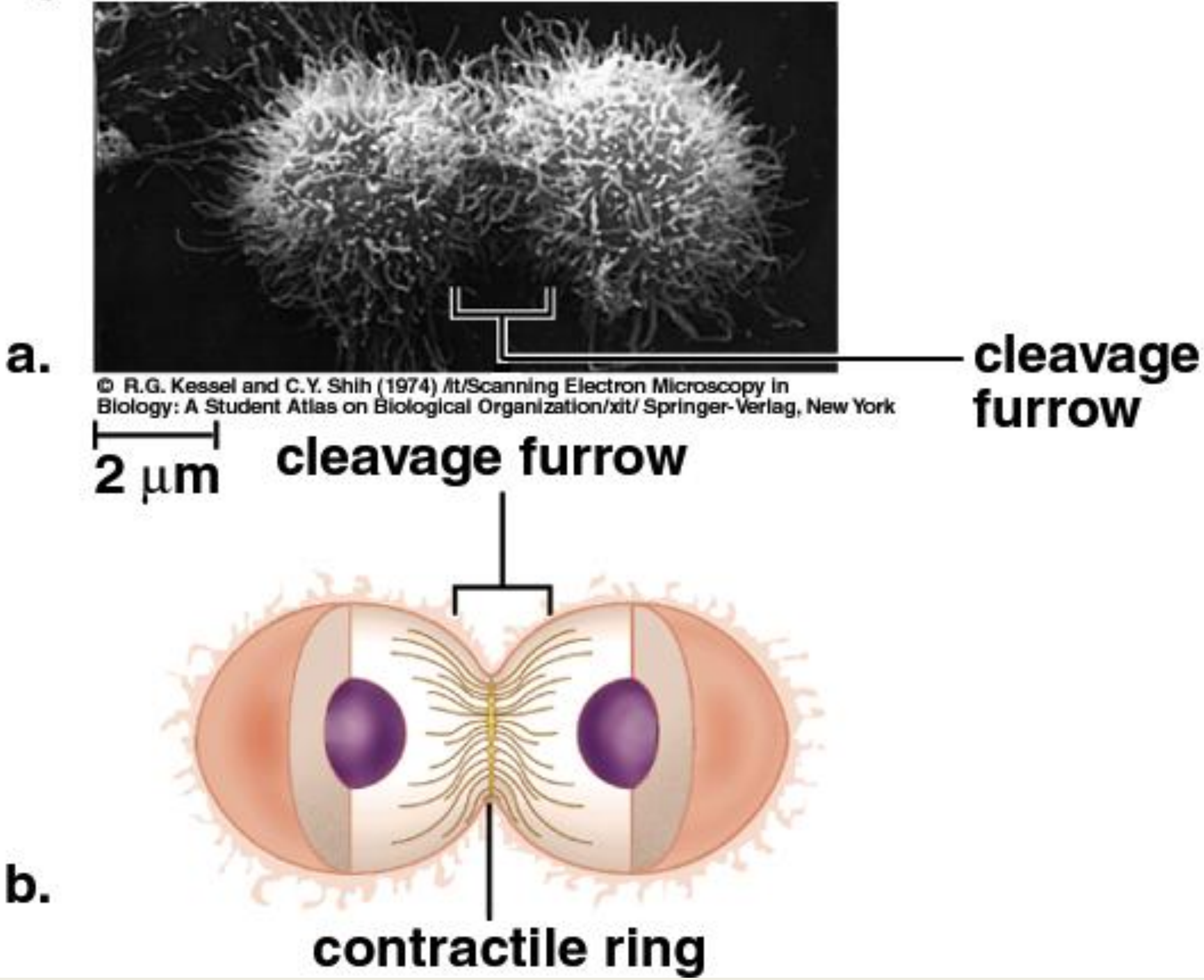


Telophase

Daughter cells are forming as nuclear envelopes and nucleoli appear.
Chromosomes will become indistinct chromatin.

Cytokinesis in animal cell



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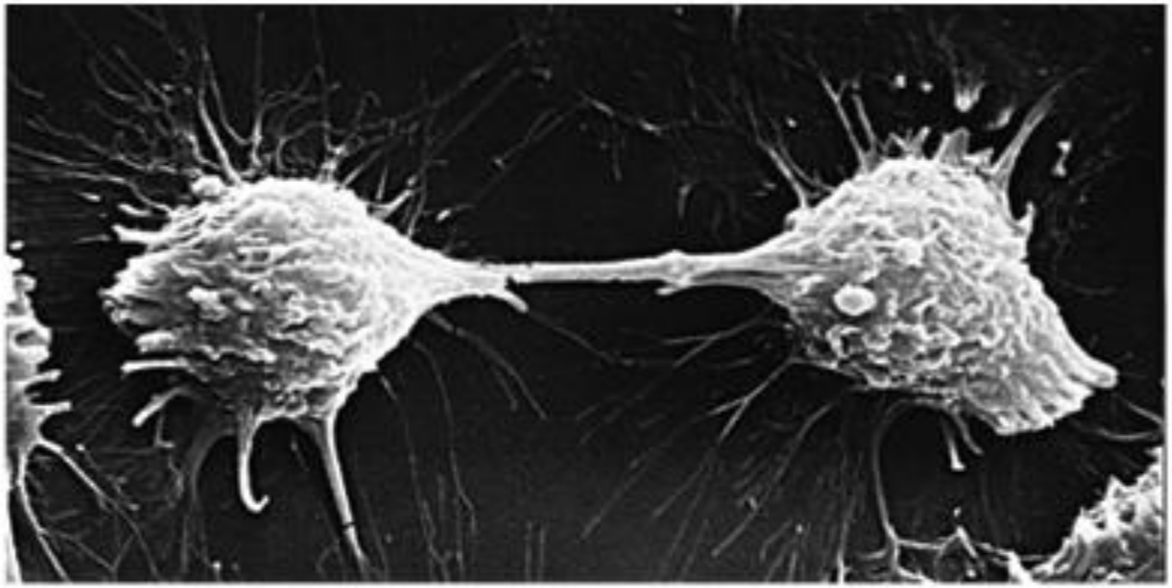
Cytokinesis in animal cell



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2 µm

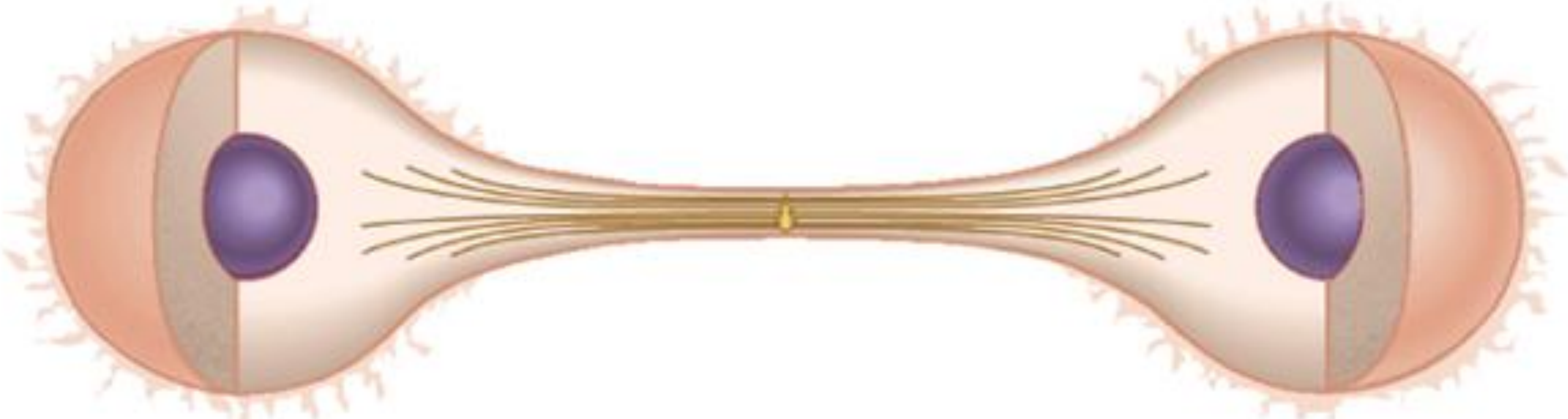
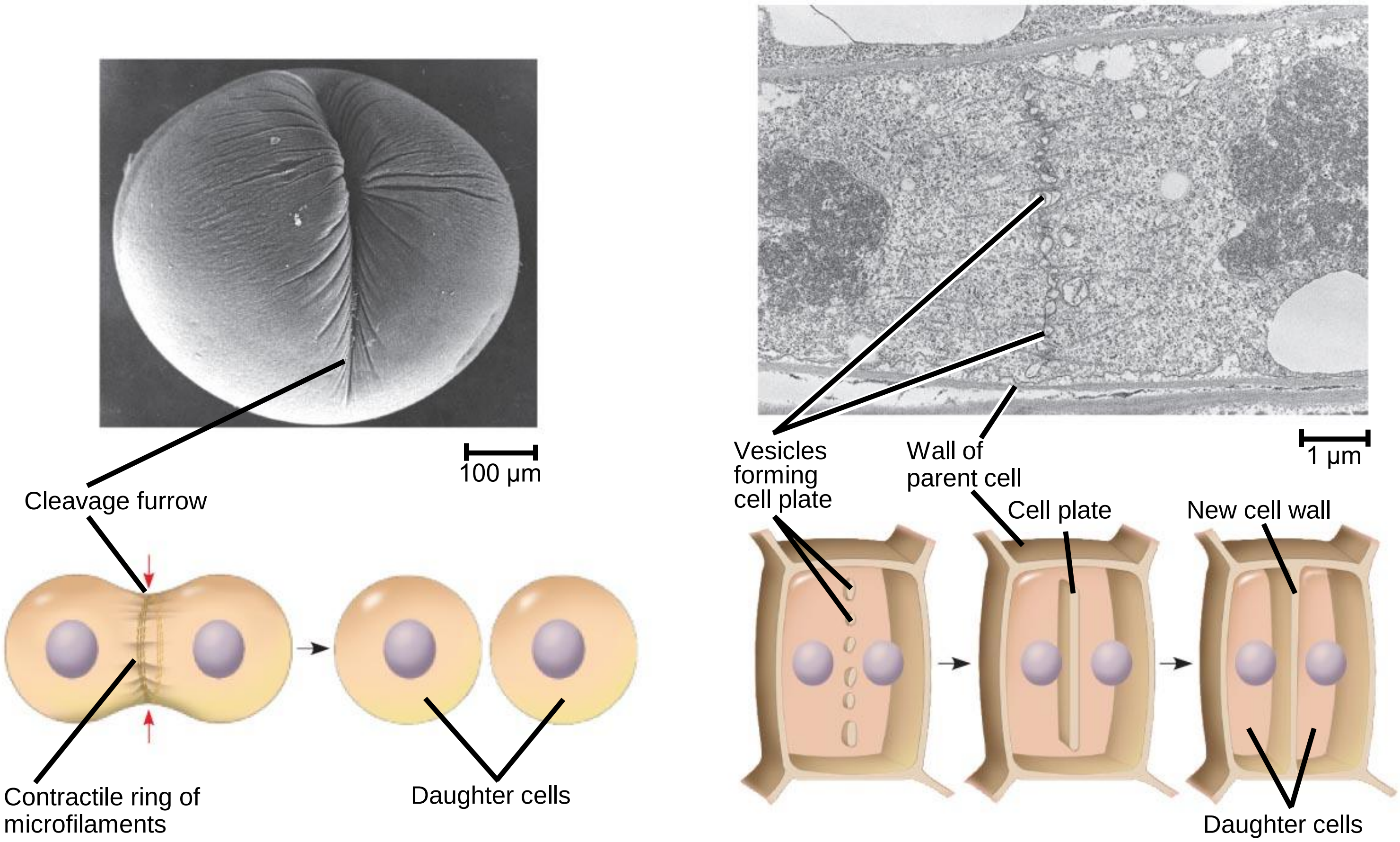


Fig. 12-9



(a) Cleavage of an animal cell (SEM)

(b) Cell plate formation in a plant cell (TEM)

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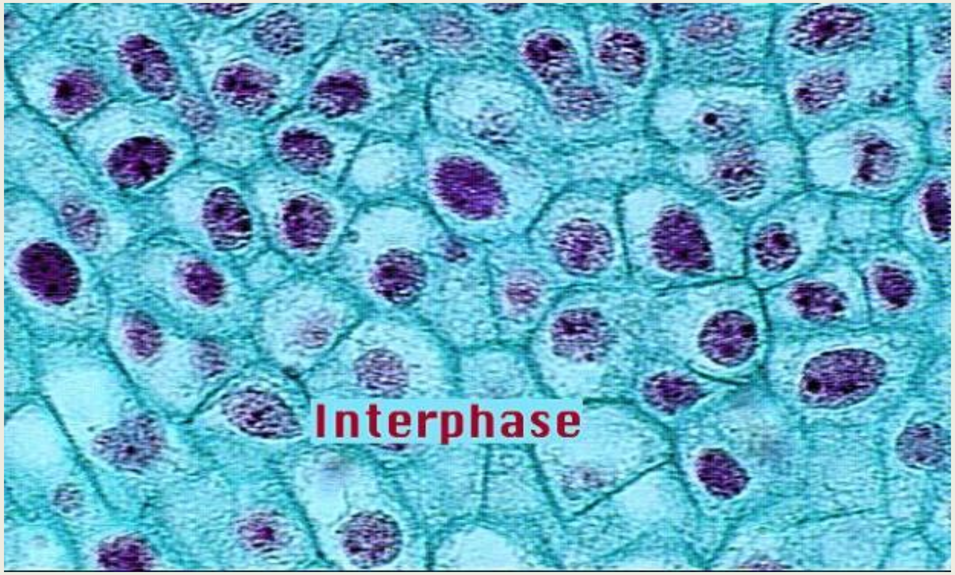
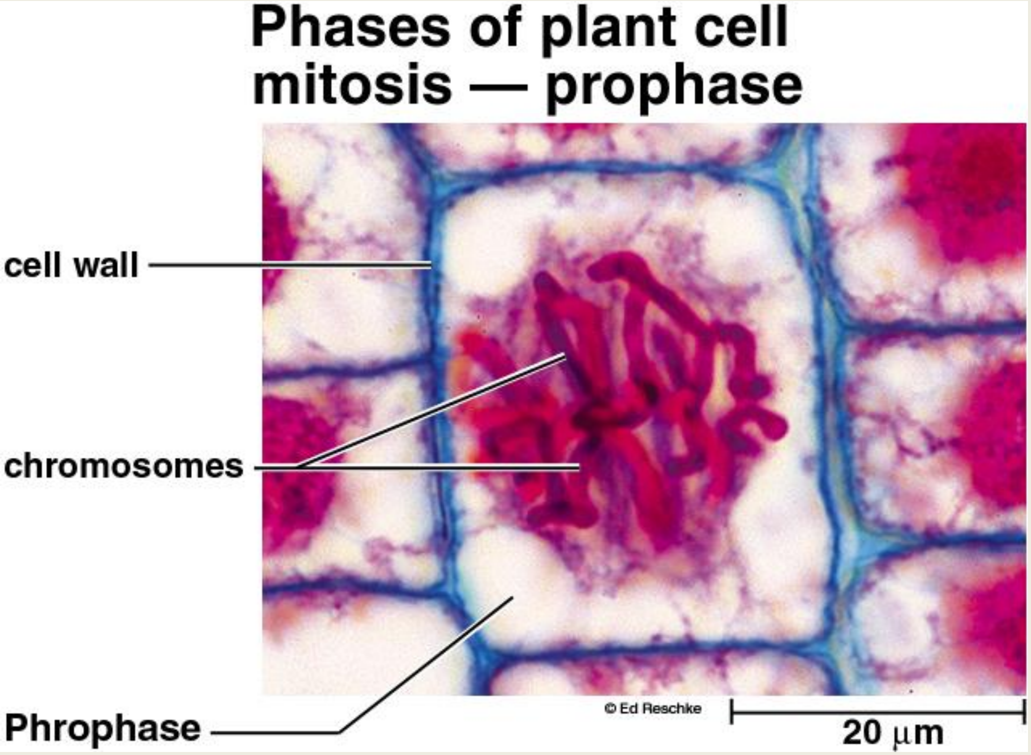
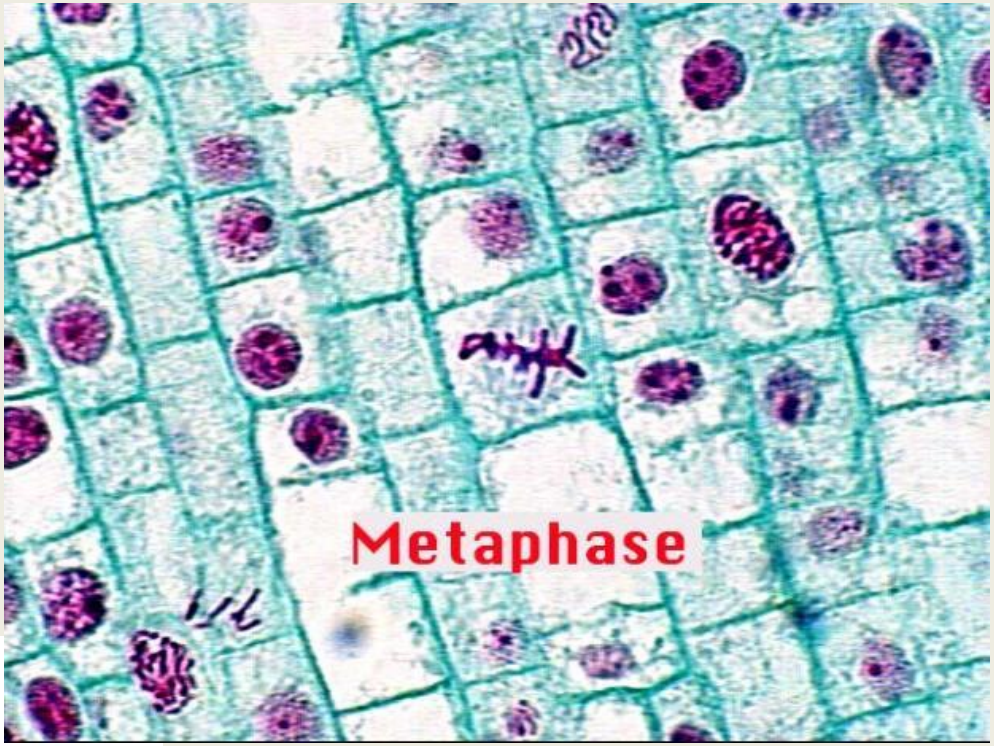
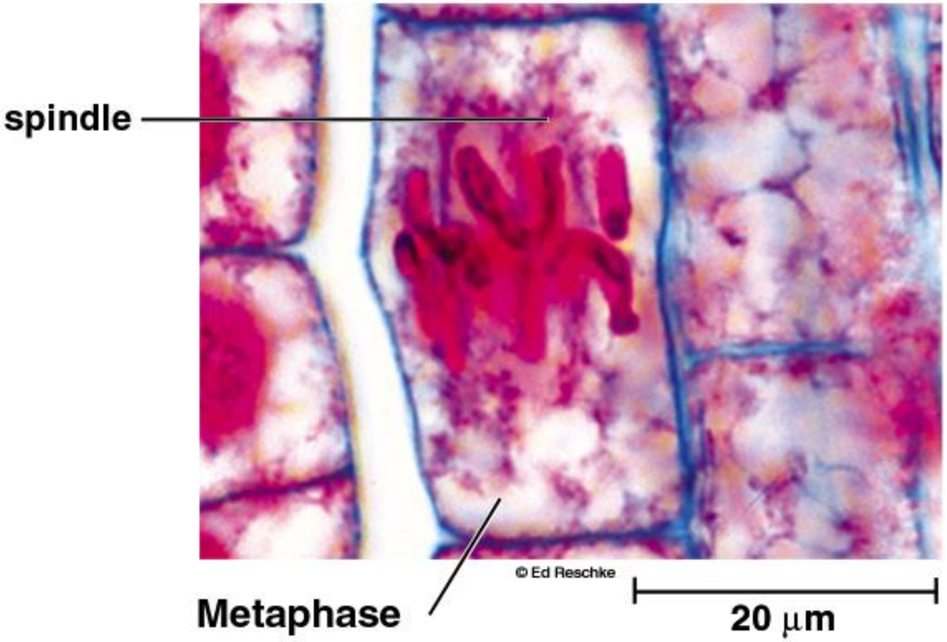
Plant cell division







Phases of plant cell mitosis — metaphase



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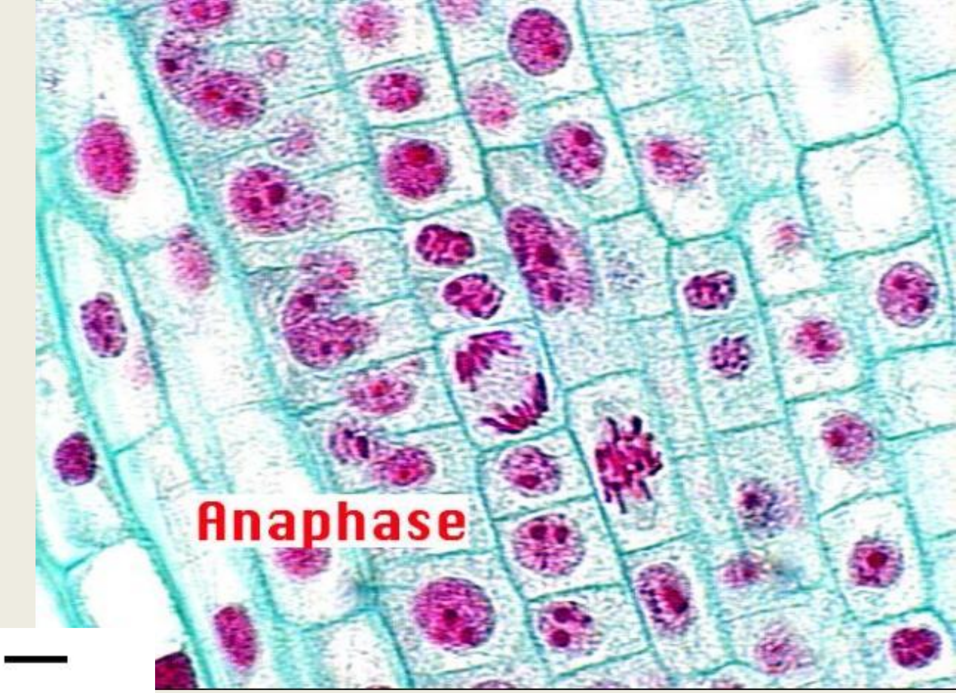
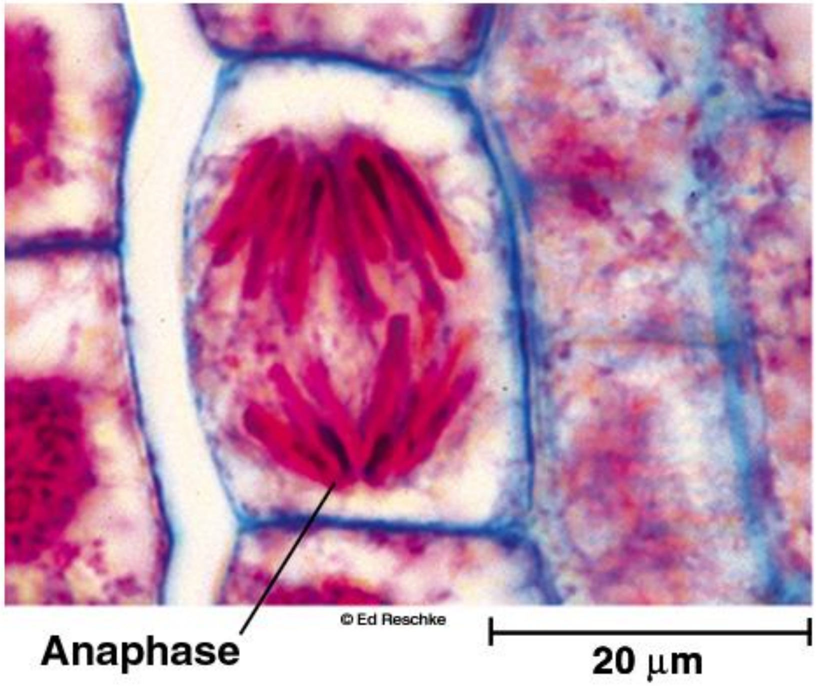
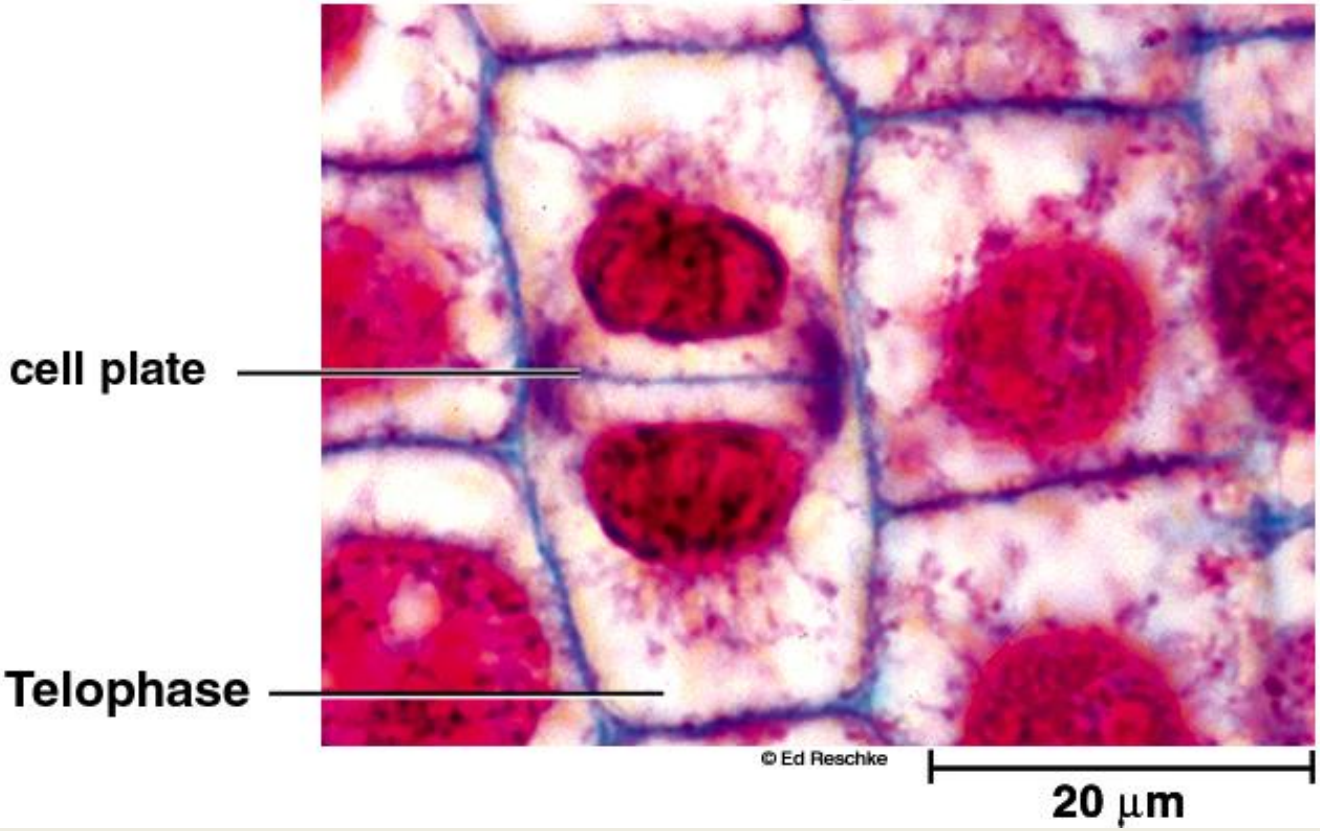


Phases of plant cell mitosis — anaphase



Phases of plant cell mitosis — telophase



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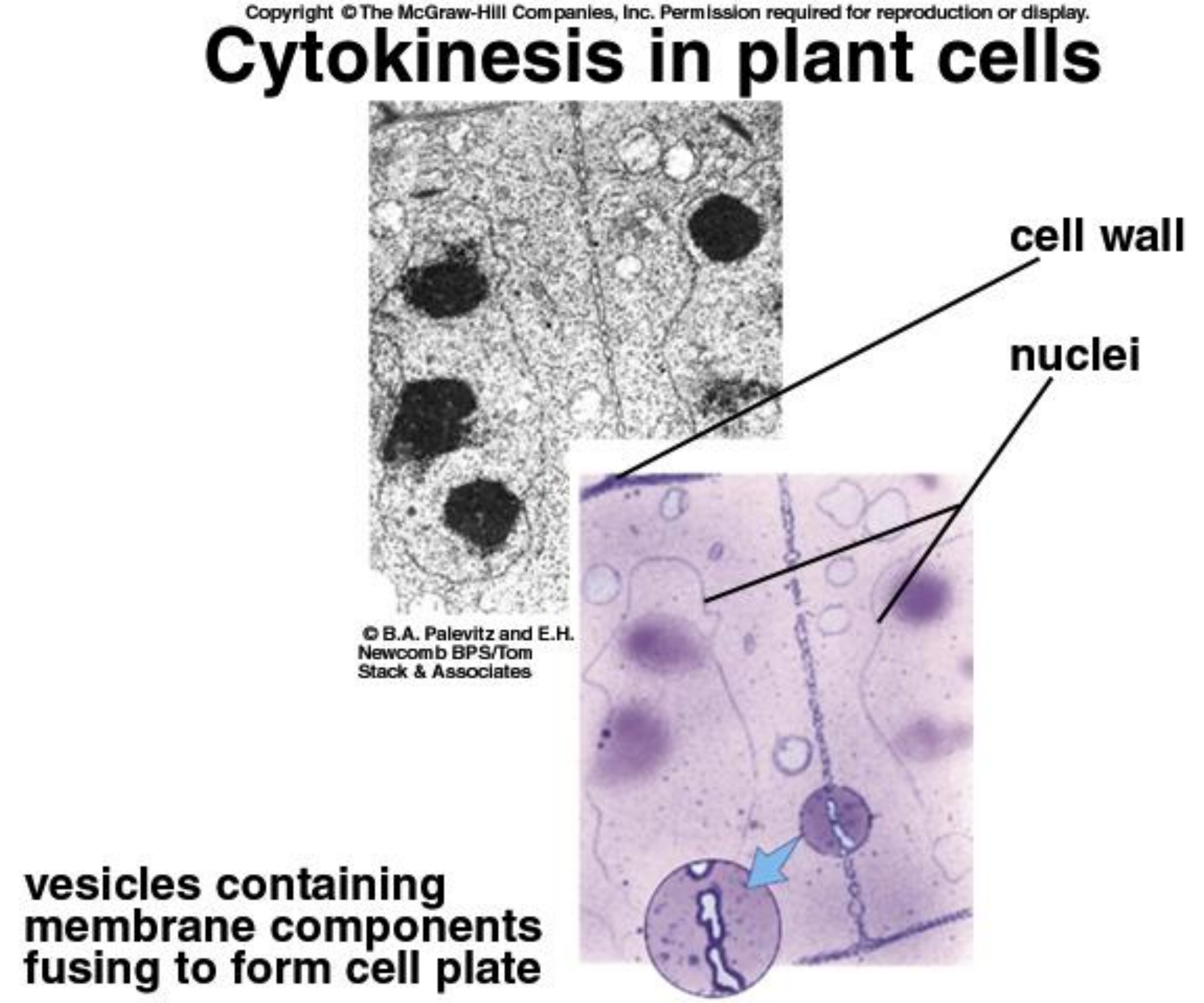
Golgi apparatus produces vesicles that move to the midpoint between the daughter cell nuclei



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Cytokinesis in plant cells

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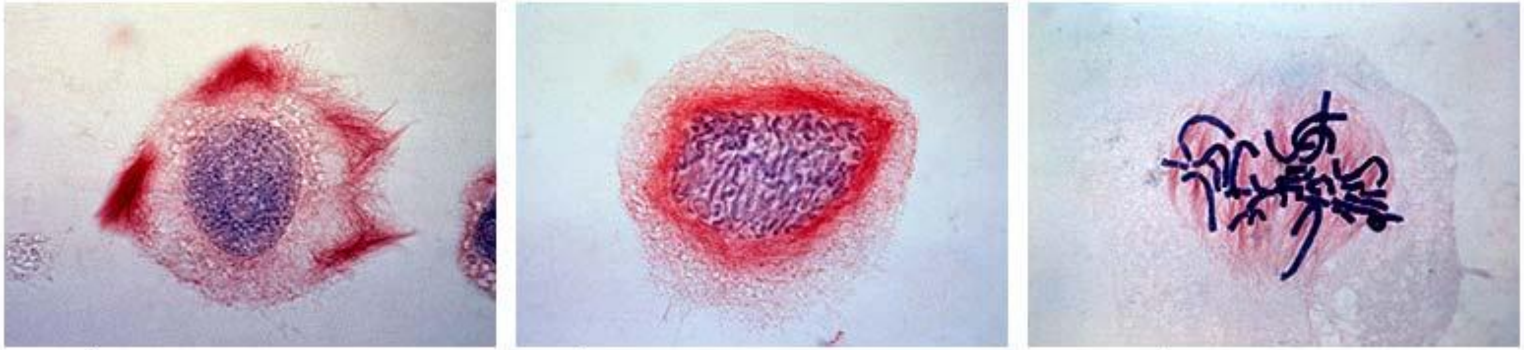
cell wall
nuclei
vesicles containing membrane components fusing to form cell plate

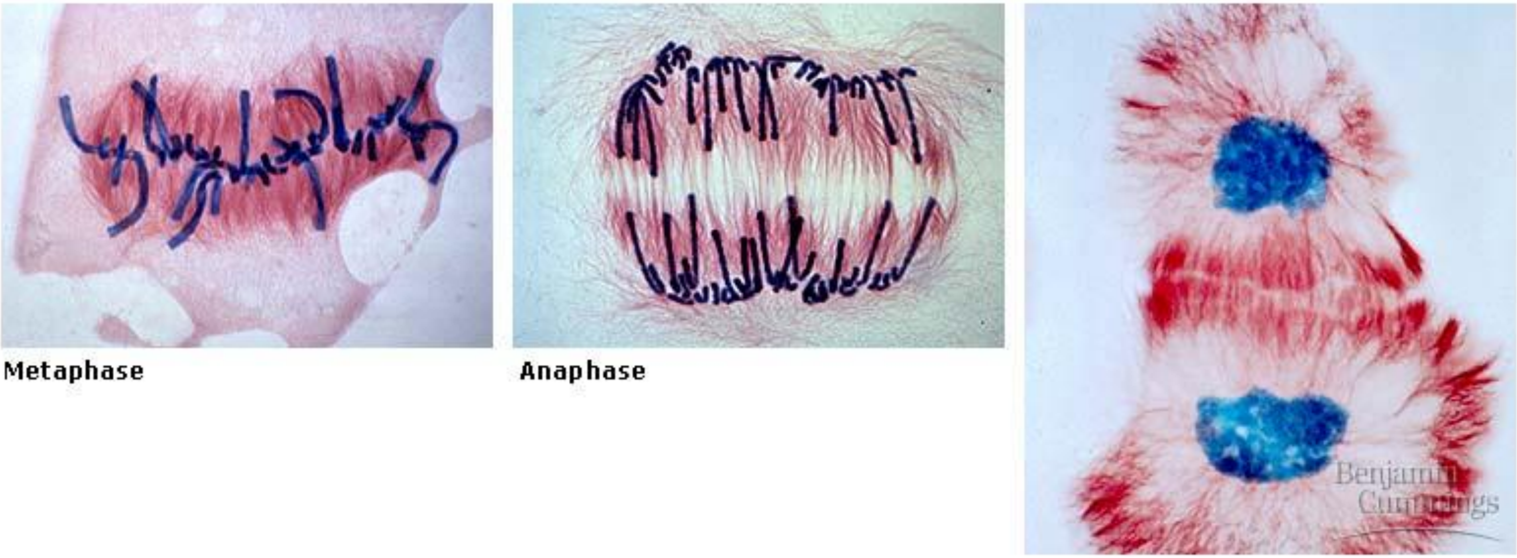
Figure 12.9 Mitosis in a plant cell



Interphase

Prophase

Prometaphase



Benjamin Cummings

Metaphase

Anaphase

Telophase

The Cell Cycle

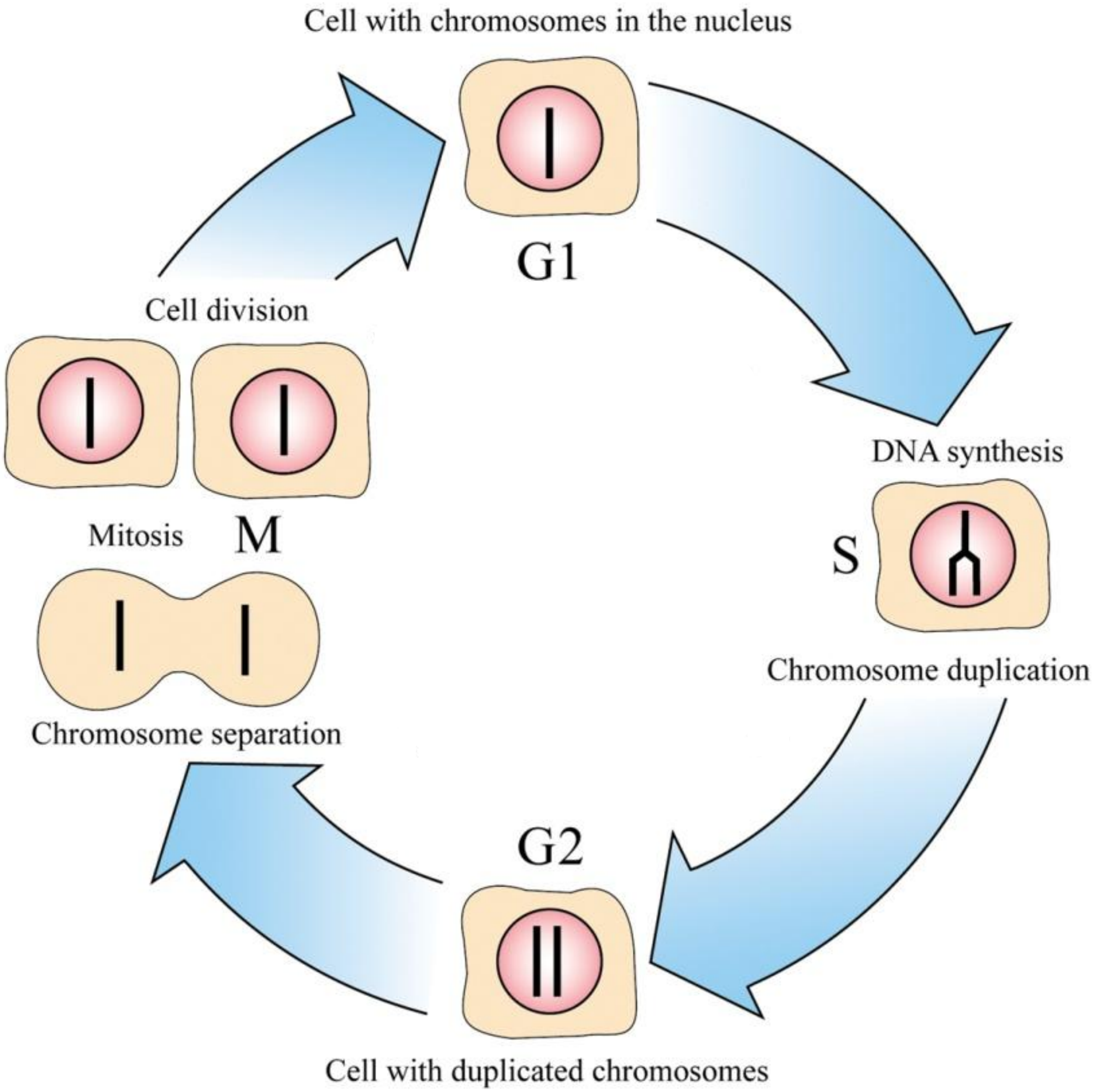
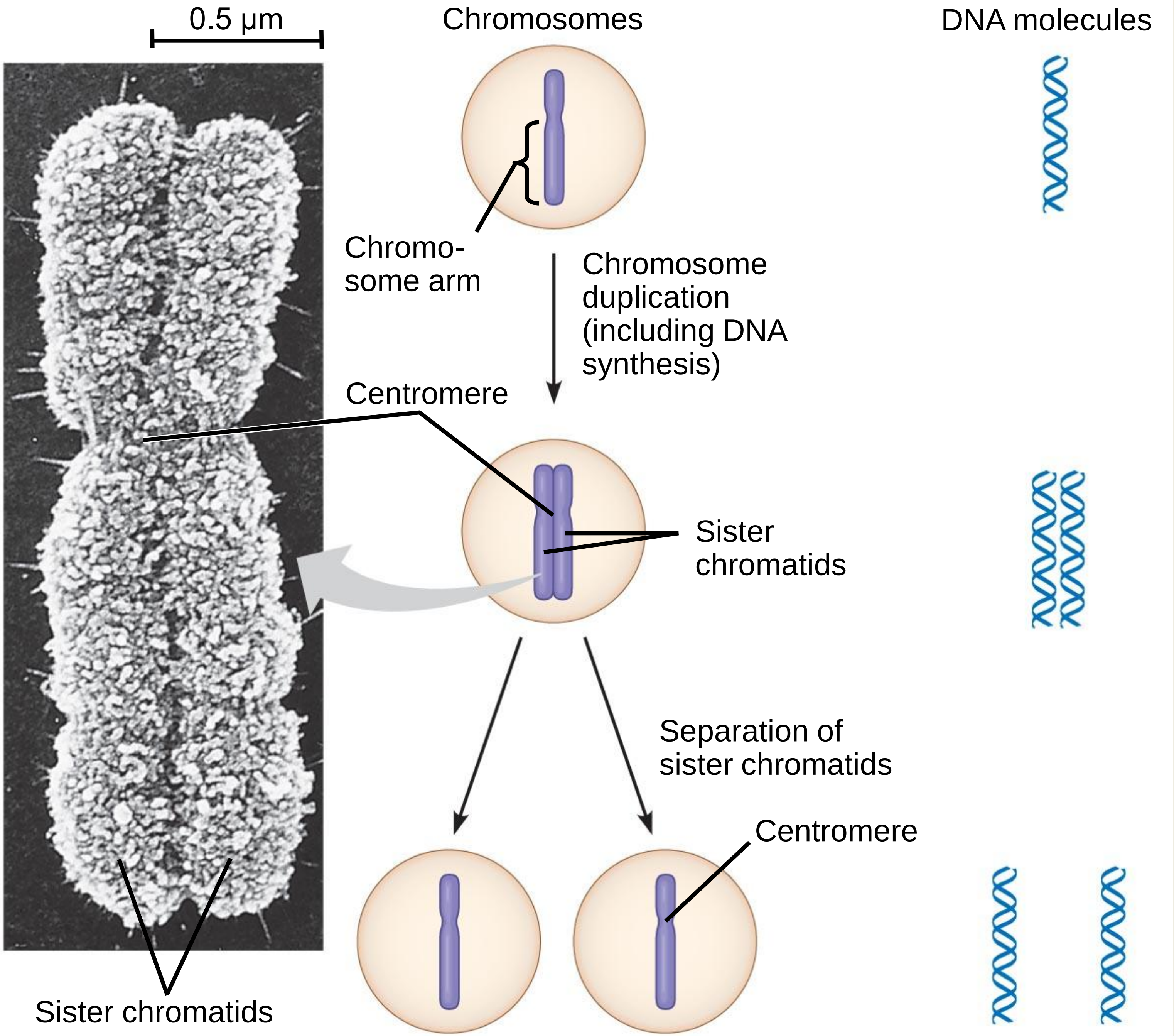


Fig. 12-4



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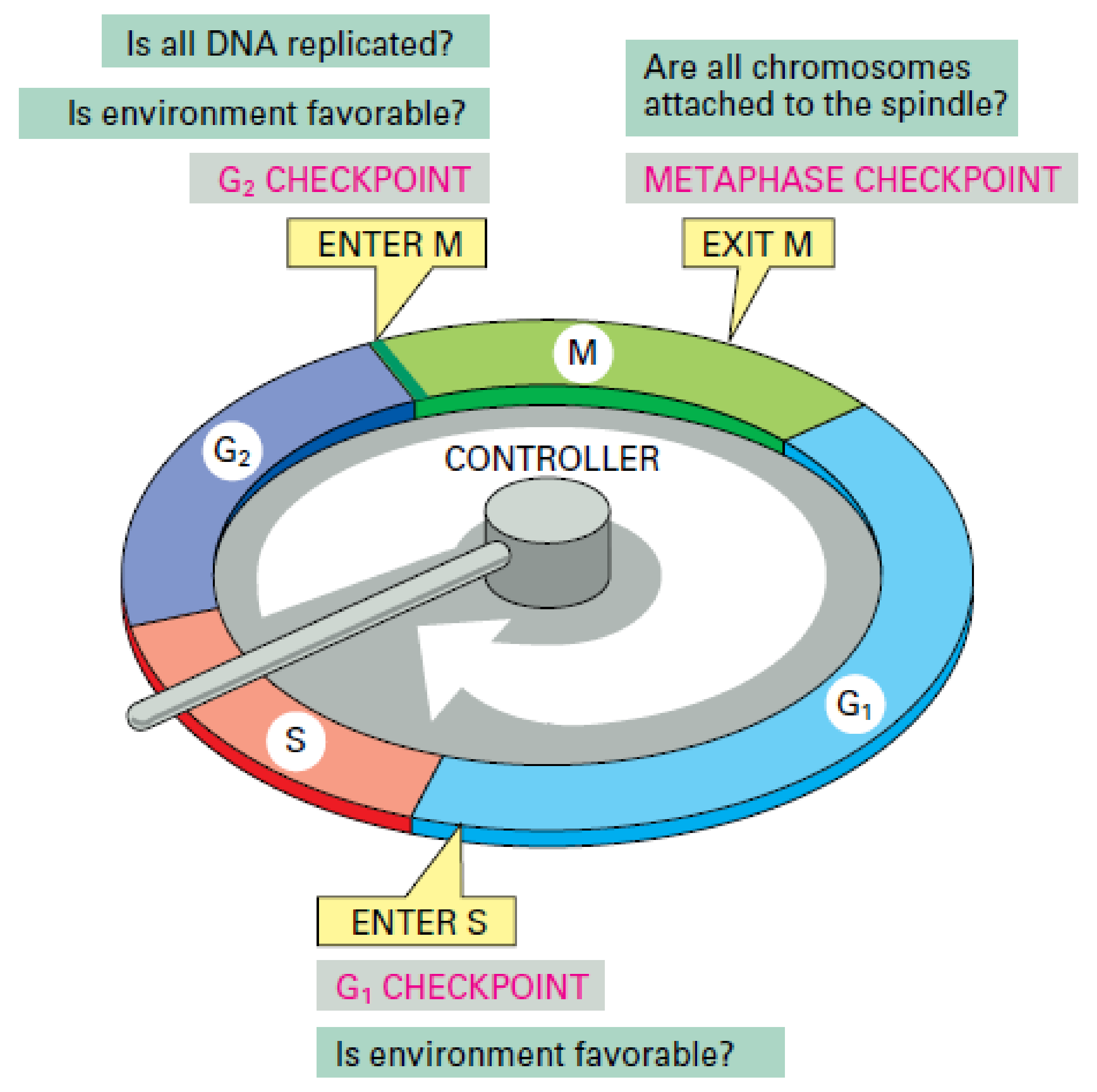
Checkpoints



The Go (G zero) state results in the dismantling of most of the replication machine. Nerve and muscle cells are in this state. Many other cells come to this important checkpoint each time after they have divided.

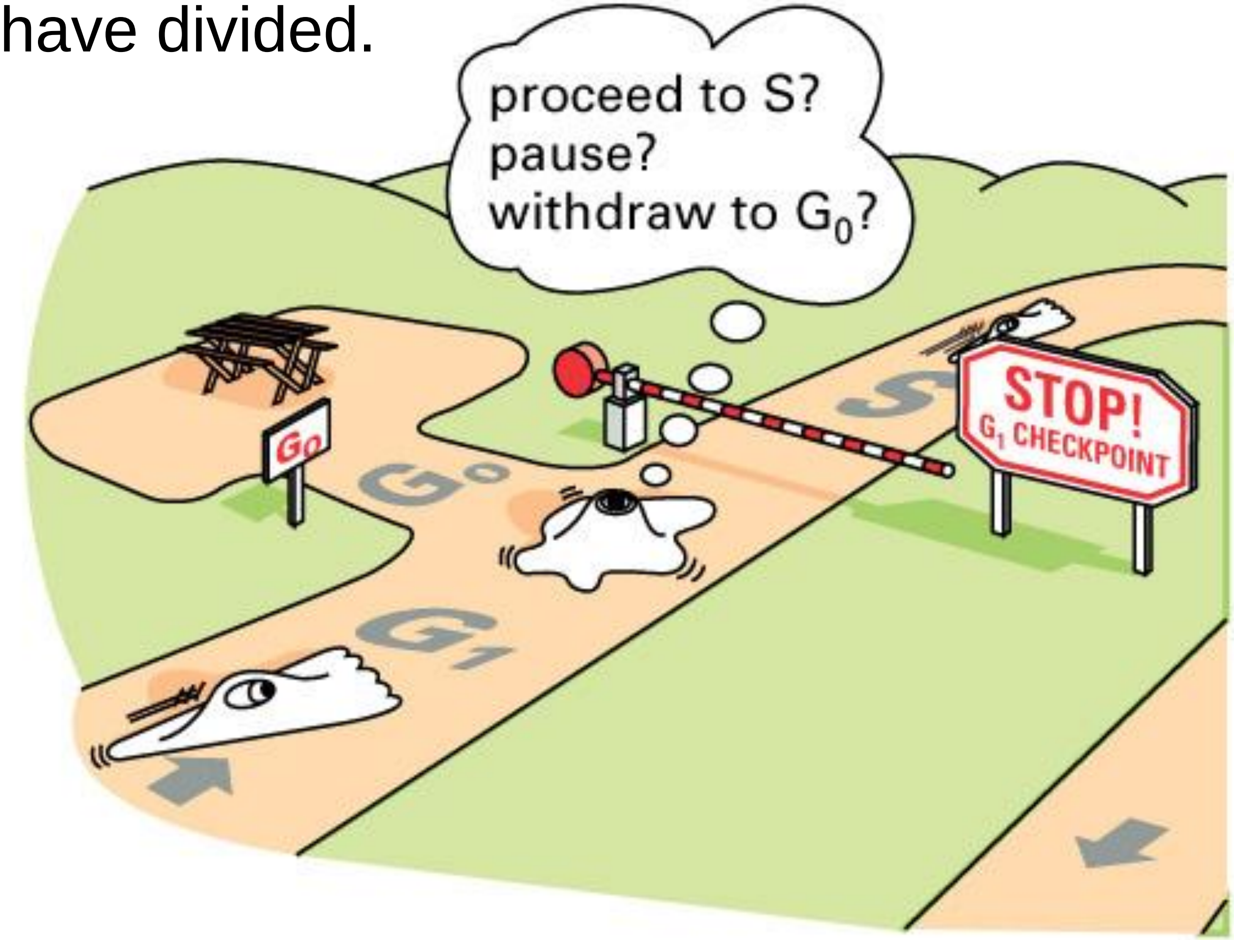


Figure 18-16 **Essential Cell Biology, 2/e. (© 2004 Garland Science)**

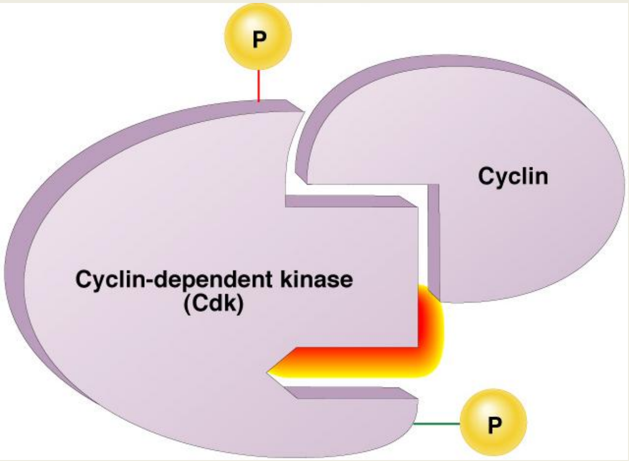
Overview of the levels of cell cycle control

- **cyclins**
- **Cdk's /**cyclin-dependent kinases
- Cdk-cyclin complex activating phosphorylation/ CAK – **CDK-activating kinase**
- **Cdk-cyclin** complex **inactivation:** kinase + phosphatases
- Cdk-cyclin complex **inhibitors – CKI**
- Cdk-cyclin complex degradation by **ubiquitin-proteolysis**

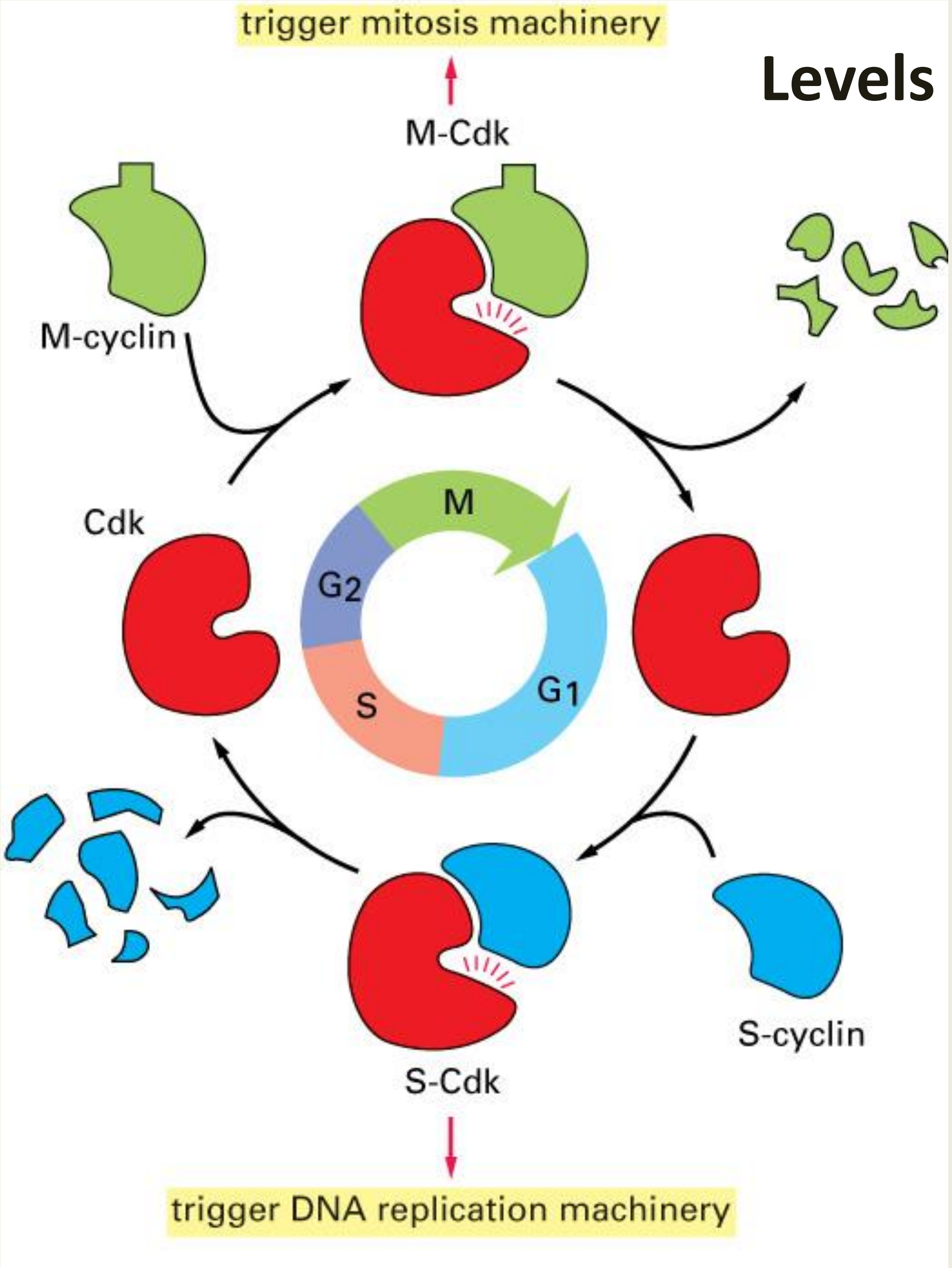
Levels of cell cycle control

- **cyclins**
  - regulatory proteins
  - levels cycle in the cell

- **Cdk's**
  - cyclin-dependent kinases
  - phosphorylate cellular proteins



Levels of cell cycle control



- **cyclins**
  - regulatory proteins
  - levels cycle in the cell
- **Cdk’s**
  - cyclin-dependent kinases
  - phosphorylate cellular proteins

Основные циклины и CDK

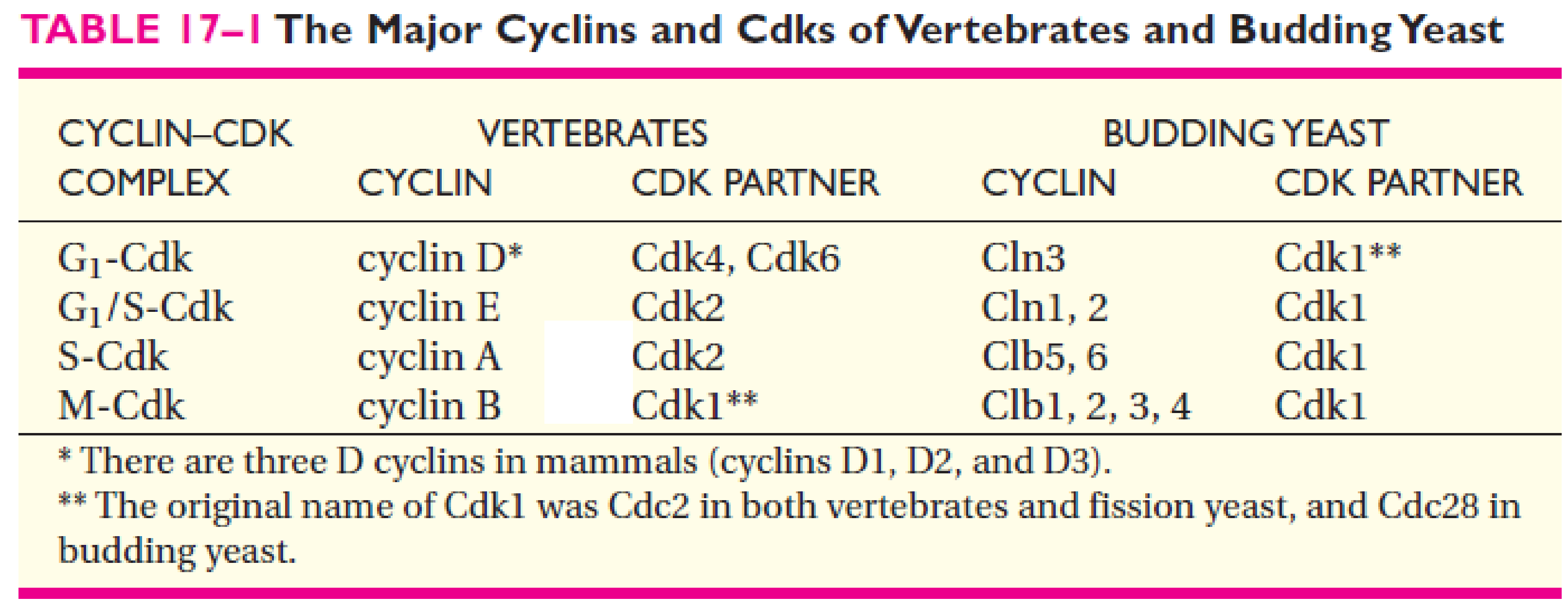


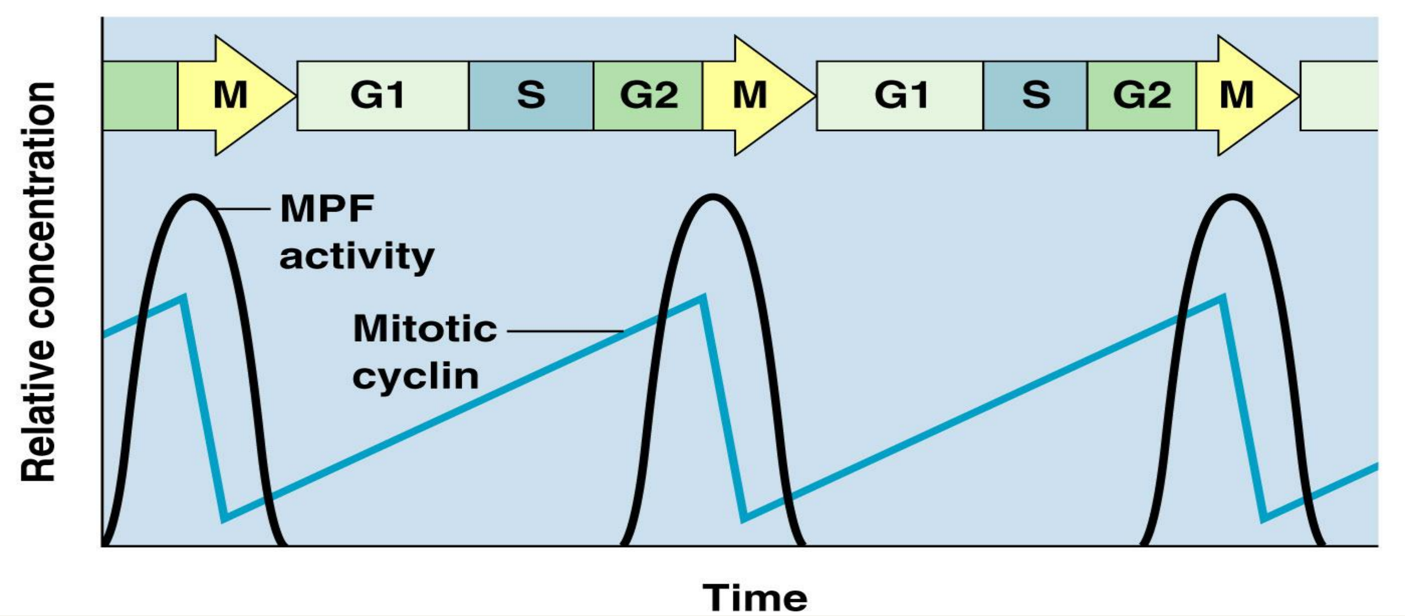
TABLE 17–1 The Major Cyclins and Cdks of Vertebrates and Budding Yeast

CYCLIN–CDK COMPLEX	VERTEBRATES CYCLIN	VERTEBRATES CDK PARTNER	BUDDING YEAST CYCLIN	BUDDING YEAST CDK PARTNER
G_1-Cdk	cyclin D*	Cdk4, Cdk6	Cln3	Cdk1**
G_1/S-Cdk	cyclin E	Cdk2	Cln1, 2	Cdk1
S-Cdk	cyclin A	Cdk2	Clb5, 6	Cdk1
M-Cdk	cyclin B	Cdk1**	Clb1, 2, 3, 4	Cdk1

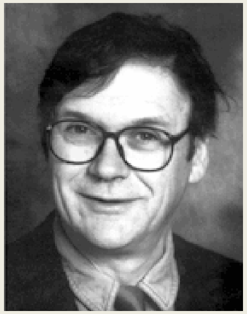
* There are three D cyclins in mammals (cyclins D1, D2, and D3).

** The original name of Cdk1 was Cdc2 in both vertebrates and fission yeast, and Cdc28 in budding yeast.

Cyclins & Cdks 1970-80 | 2001



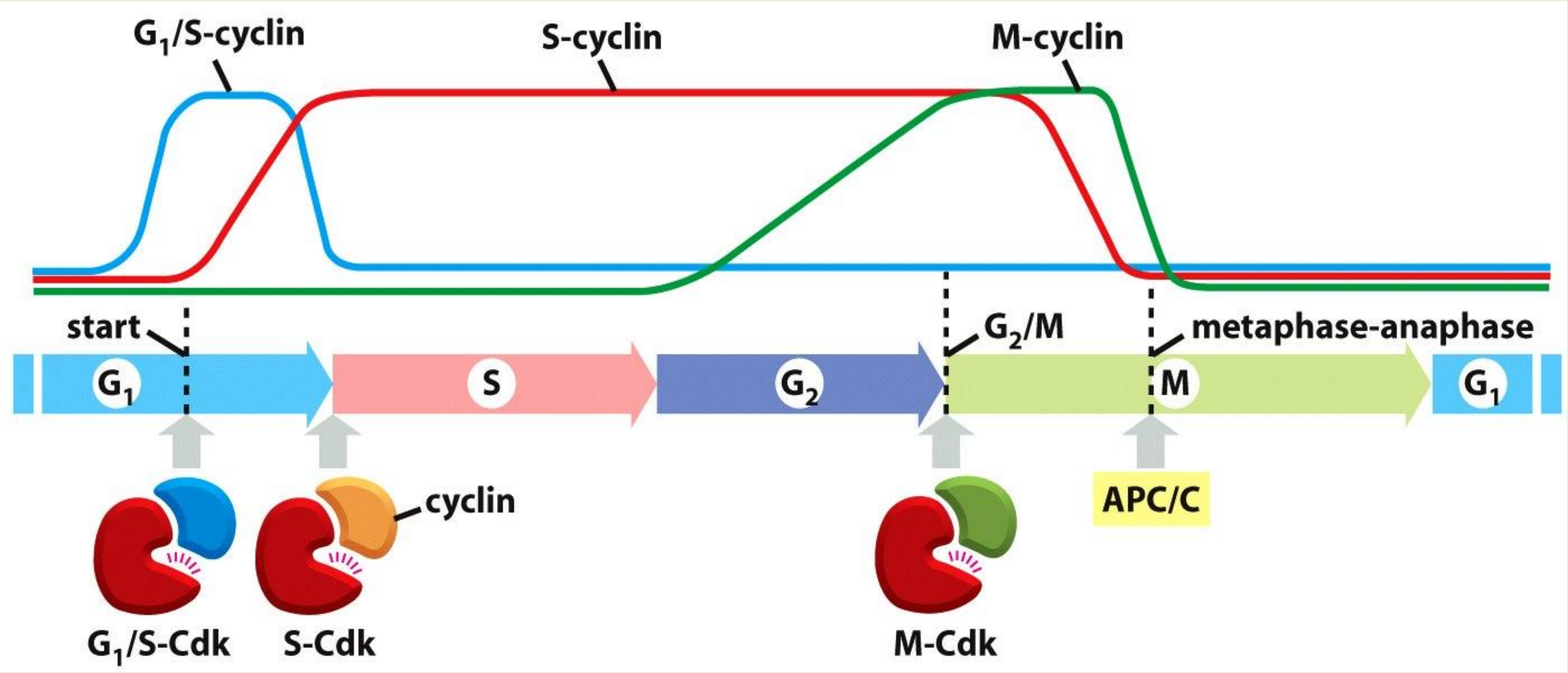
Leland H. Hartwell
checkpoints



Tim Hunt
Cdks

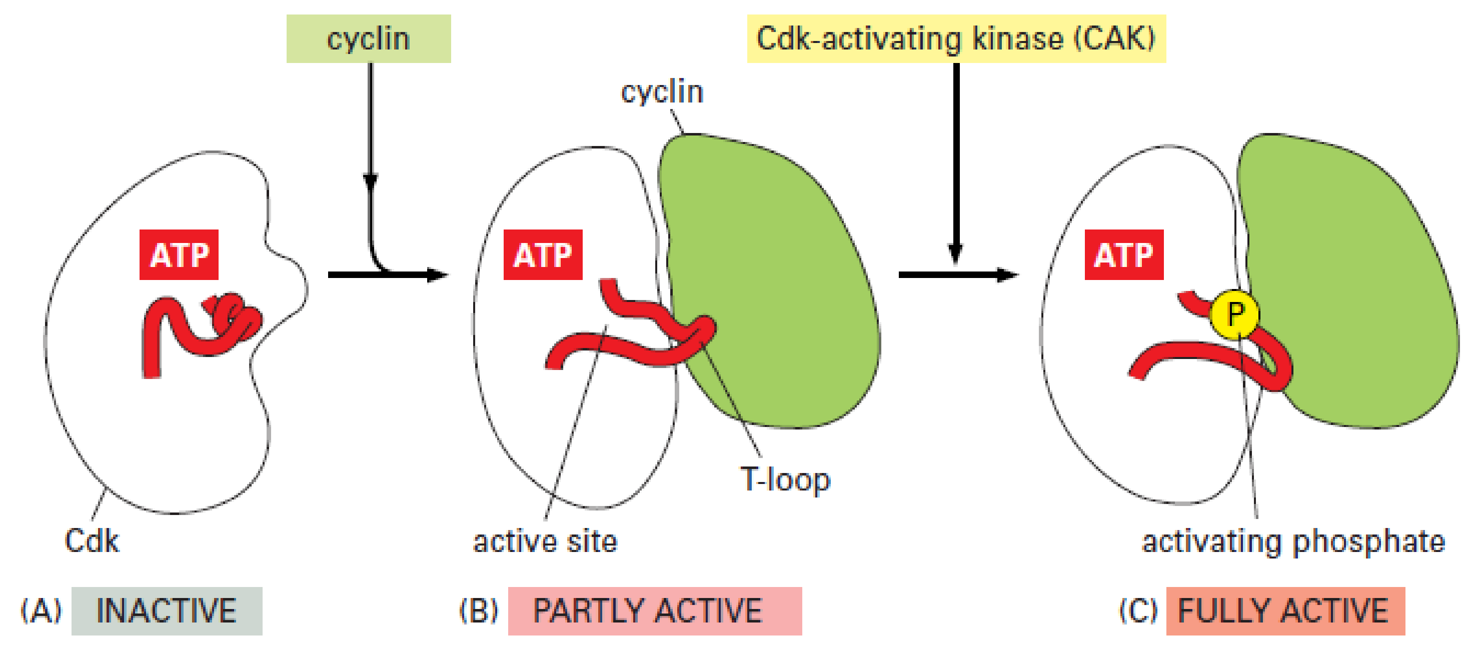
Sir Paul Nurse
cyclins

Overview of Cell Cycle Events



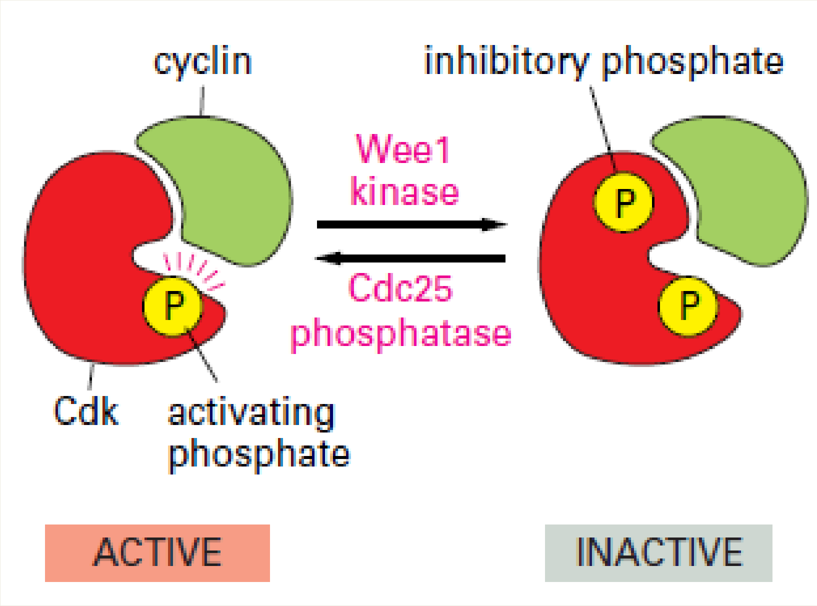
Levels of cell cycle control

- Cdk-cyclin complex activating phosphorylation
  - CAK – **CDK-activating kinase**



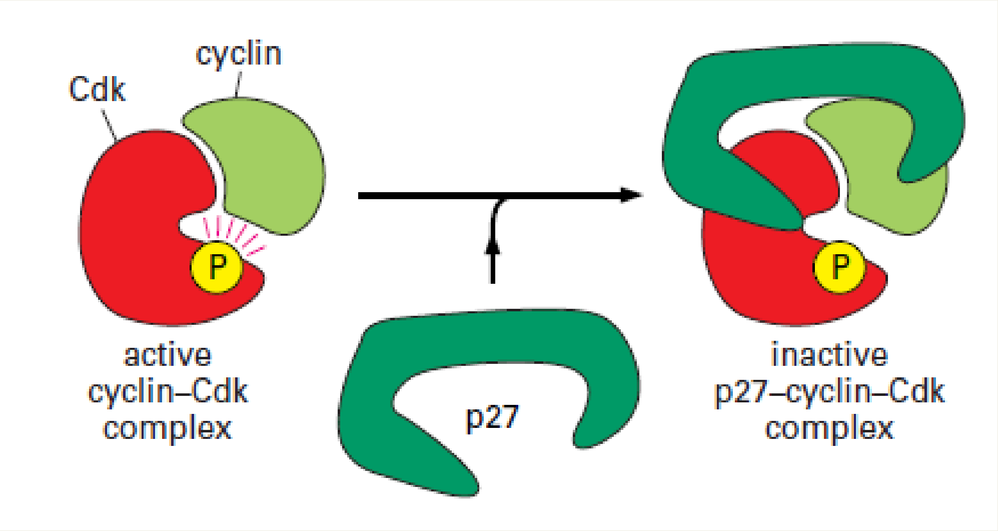
Levels of cell cycle control

- **Cdk-cyclin** complex **inactivation**
  - CDK-Tyr-Thr-kinase
  - Cdc25 family of phosphatases



Levels of cell cycle control

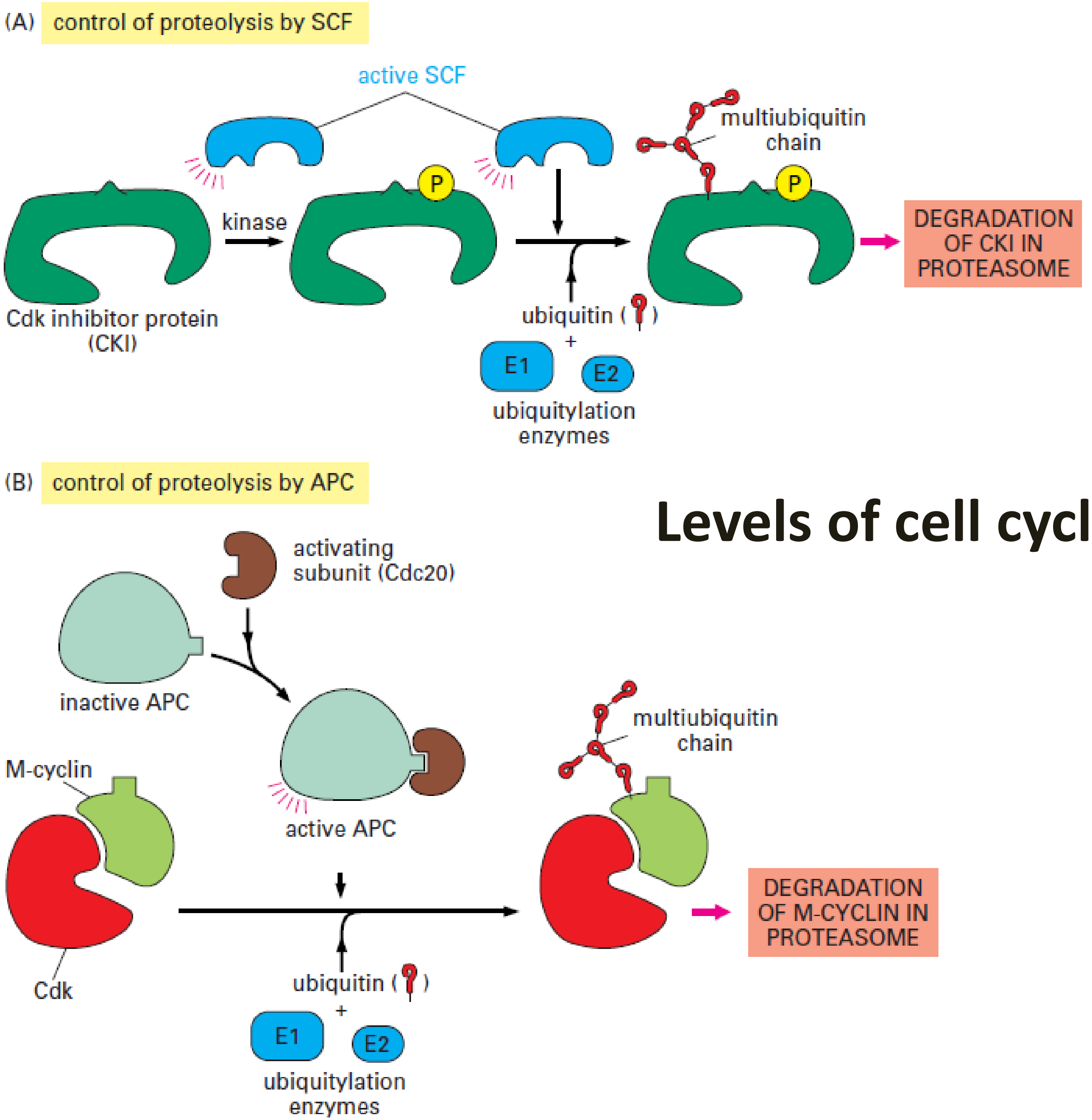
- Cdk-cyclin complex **inhibitors - CKI**
  - p21; p27; p57
  - p16; p15; p18; p19



Levels of cell cycle control: Cdk-cyclin complex degradation by **ubiquitin-proteolysis**

- SCF (after its three main protein subunits) is responsible for the ubiquitylation and destruction of G1/S-cyclins and certain CKI proteins that control S-phase initiation.
- In M phase, the anaphase-promoting complex (APC) is responsible for the ubiquitylation and proteolysis of M-cyclins and other regulators of mitosis

Levels of cell cycle control


(A) control of proteolysis by SCF
active SCF
multiubiquitin chain
P
kinase
P
DEGRADATION OF CKI IN PROTEASOME
Cdk inhibitor protein (CKI)
ubiquitin ( )
+
E1
E2
ubiquitylation enzymes
(B) control of proteolysis by APC
activating subunit (Cdc20)
inactive APC
multiubiquitin chain
M-cyclin
active APC
DEGRADATION OF M-CYCLIN IN PROTEASOME
Cdk
ubiquitin ( )
+
E1
E2
ubiquitylation enzymes

Levels of cell cycle control

- **cyclins**
  - regulatory proteins
  - levels cycle in the cell

- **Cdk’s**
  - cyclin-dependent kinases
  - phosphorylate cellular proteins

- Cdk-cyclin complex activating phosphorylation
  - CAK – **CDK-activating kinase**

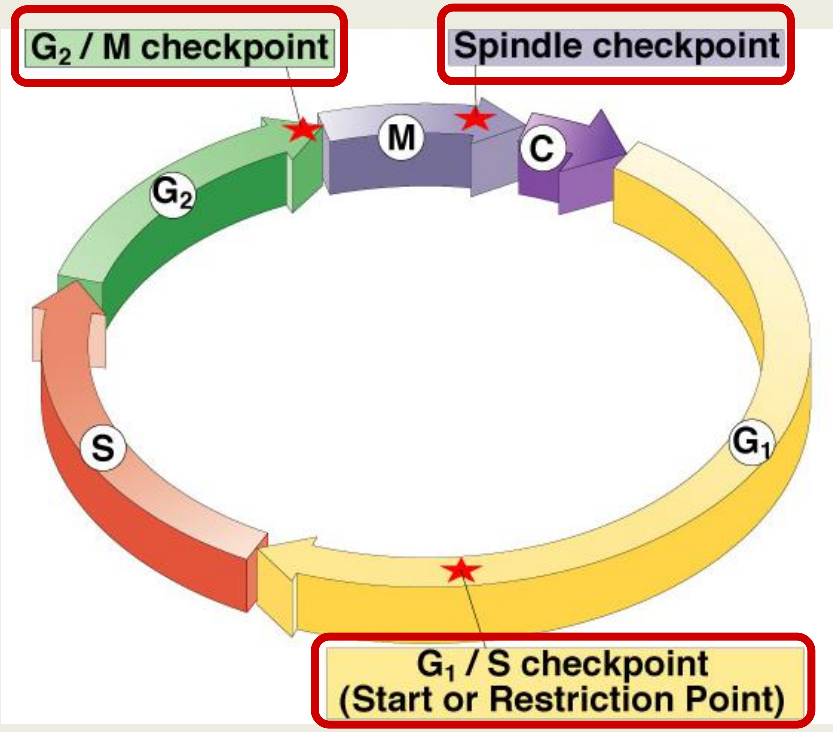
- **Cdk-cyclin** complex **inactivation**
  - CDK-Tyr-Thr-kinase
  - Cdc25 family of phosphatases

- Cdk-cyclin complex **inhibitors - CKI**
  - p21; p27; p57
  - p16; p15; p18; p19

- Cdk-cyclin complex degradation by **ubiquitin-proteolysis**

Checkpoint control system

- 3 major checkpoints:
  - G_1/S
    - can DNA synthesis begin?
  - G_2/M
    - has DNA synthesis been completed correctly?
    - commitment to mitosis
  - spindle checkpoint
    - are all chromosomes attached to spindle?
    - can sister chromatids separate correctly?

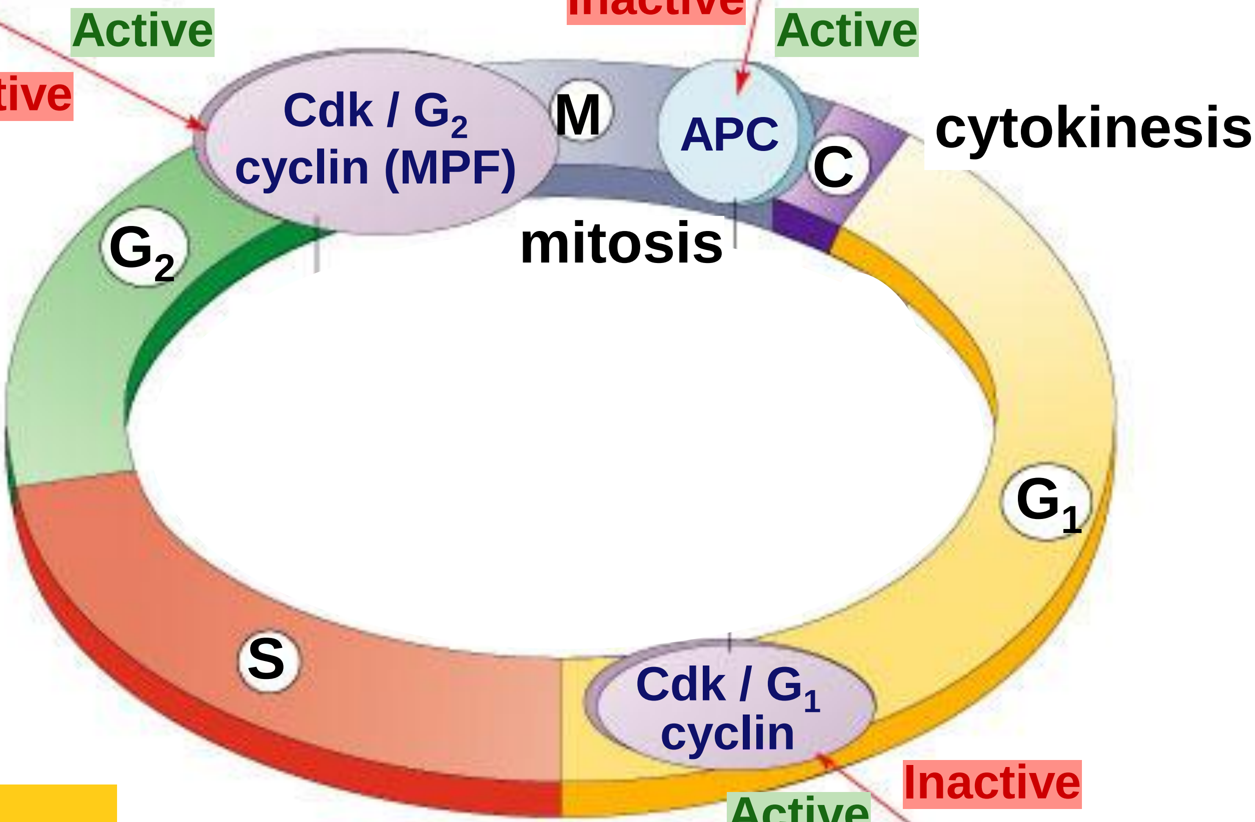


G_2 / M checkpoint

- Replication completed
- DNA integrity

Spindle checkpoint

Chromosomes attached at metaphase plate



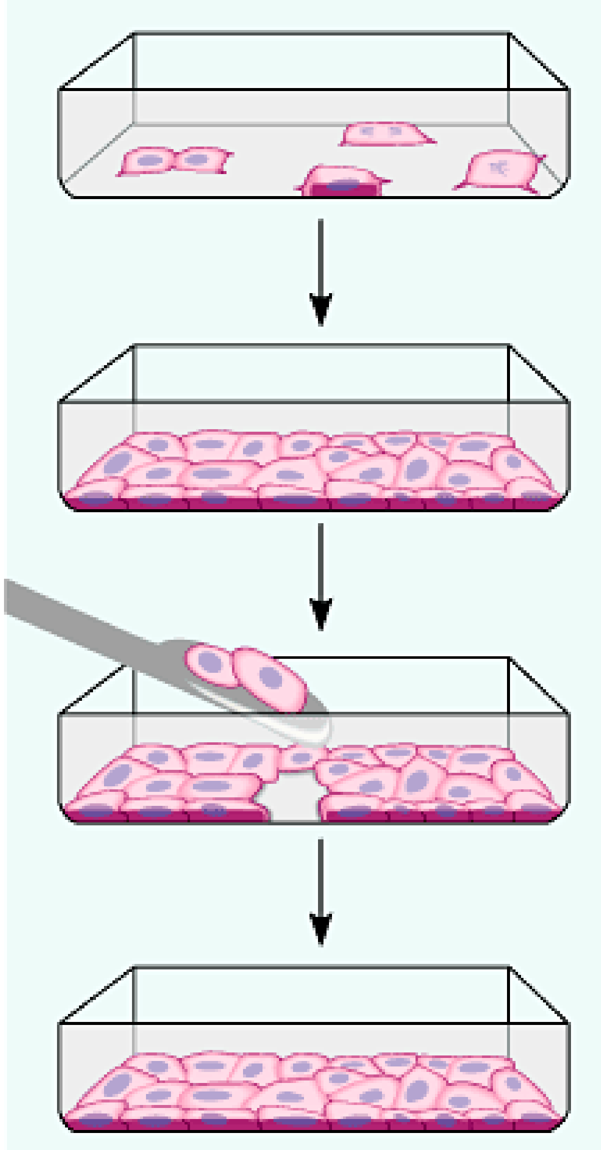
G_1 / S checkpoint

- Growth factors
- Nutritional state of cell
- Size of cell

MPF = Mitosis Promoting Factor
APC = Anaphase Promoting Complex

External signals

- Growth factors
  - – coordination between cells
  - – protein signals released by body cells that stimulate other cells to divide
    - density-dependent inhibition
      - – crowded cells stop dividing
      - – each cell binds a bit of growth factor
        - » not enough activator left to trigger division in any one cell
    - anchorage dependence
      - – to divide cells must be attached to a substrate
        - » "touch sensor" receptors

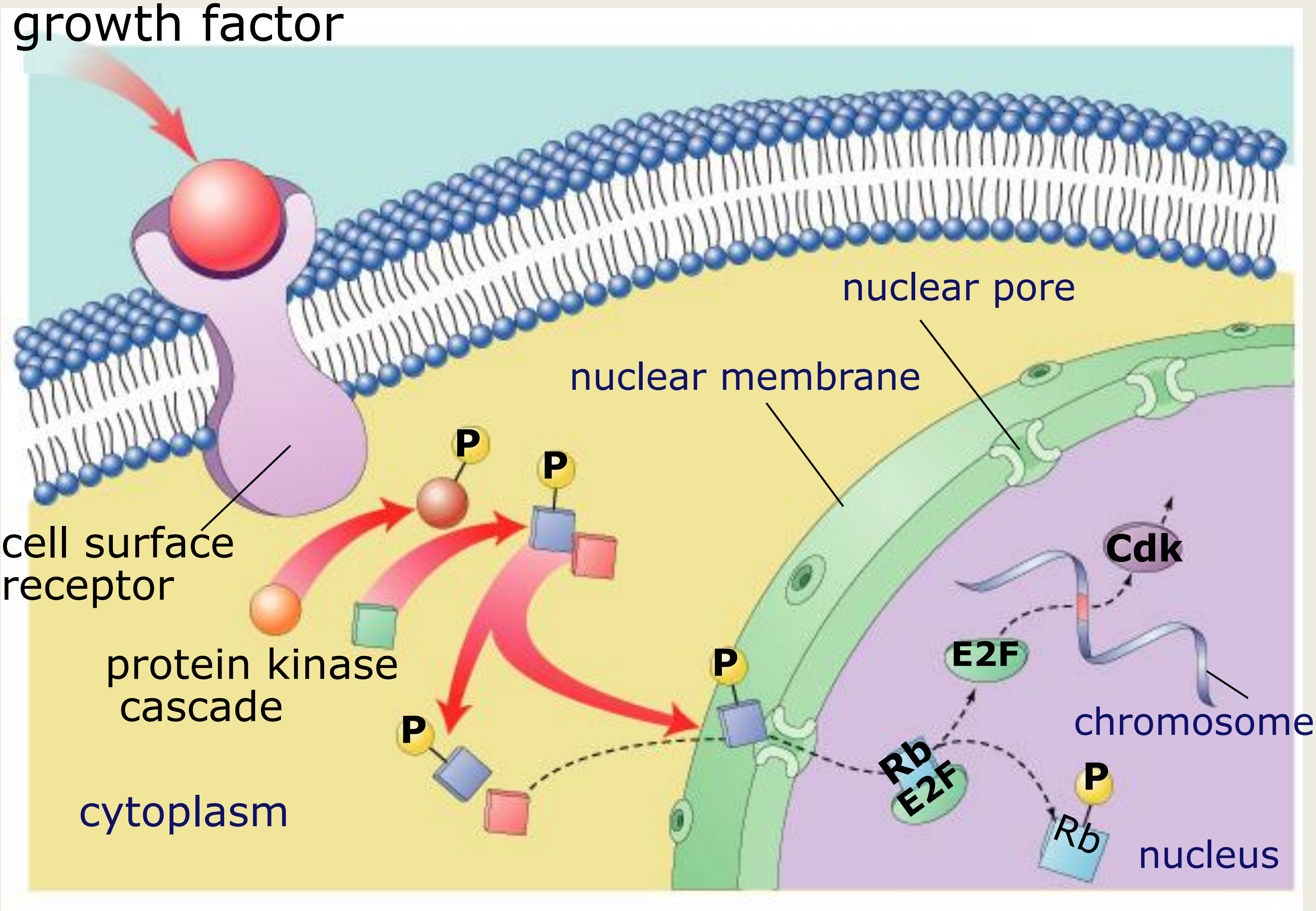


(a) Normal mammalian cells

Some growth factors :

Factor Name	**Receptor**	**Some Functions**
basic fibroblast growth factor (bFGF)	FGFRI	induces proliferation of many cells and mesoderm formation
transforming growth factor β1 (TGF-β1)	TGFβRII	inhibits growth of many cell types induces myogenesis in mouse ES cells
activin-A	ACTRIIB	induces mesoderm formation in embryo development
bone morphogenic protein 4 (BMP4)	BMPRII	differentiation of chondrocytes and osteoblasts
hepatocyte growth factor (HGF)	c-MET	induces proliferation of hepatocites
epidermal growth factor (EGF)	EGFR	induces prolifaration of mesenchymal, glial and epithelial cells
β nerve growth factor (βNGF)	NGFR	promotes neuron outgrowth
retinoic acid (RA)	RARα	induces neurons in mouse ES cells

Growth factor signals



Proteins synthesized in G_1 phase

- Energy generating
- Ribosomal
- Isoprenoid synthesis for Ras-activating (farnesyl)
- DNA-synthesis (polymerases, helicases, etc)
- Histones
- Kinases and cyclins (specific for G1)

Start of S-phase through Rb inactivation

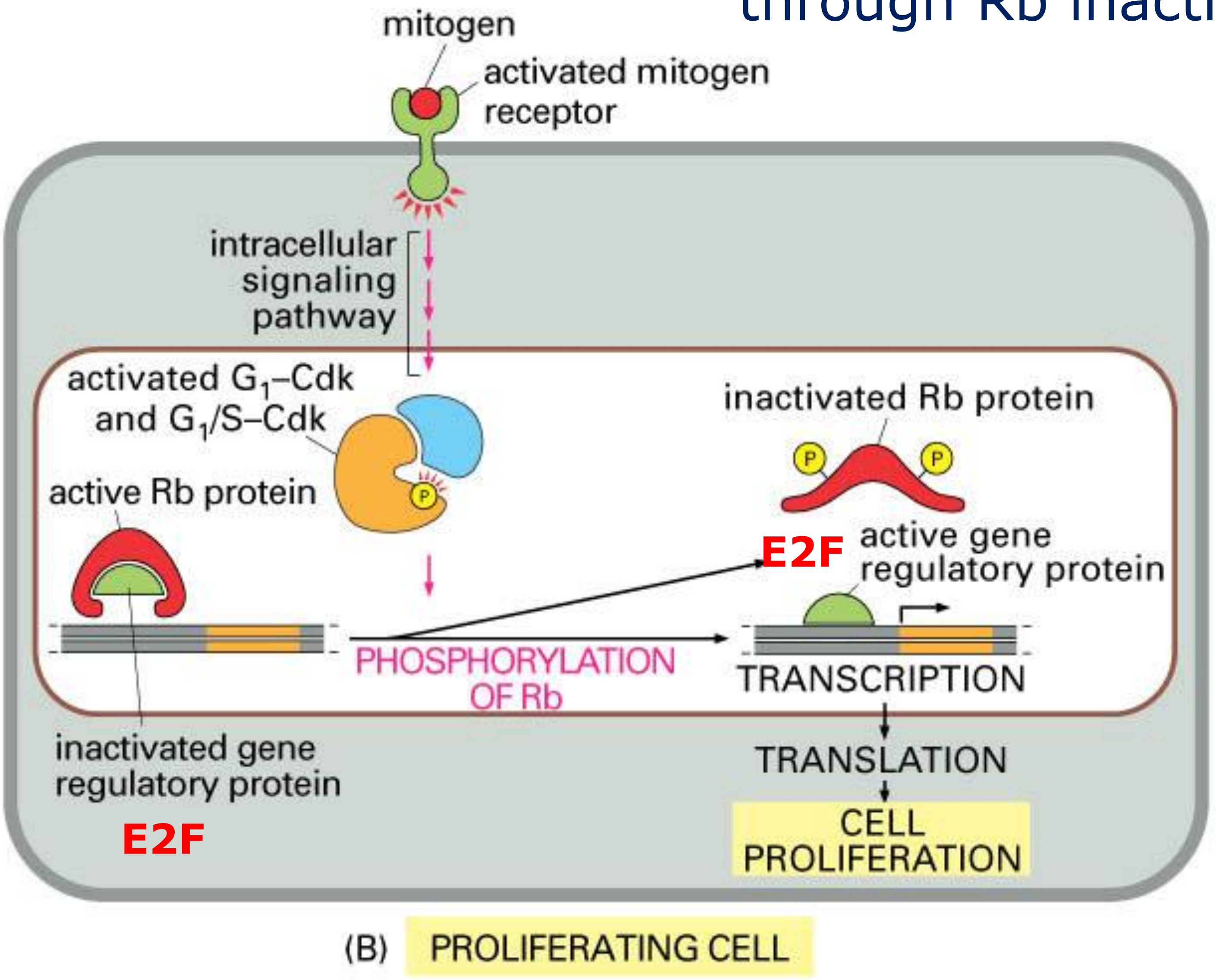
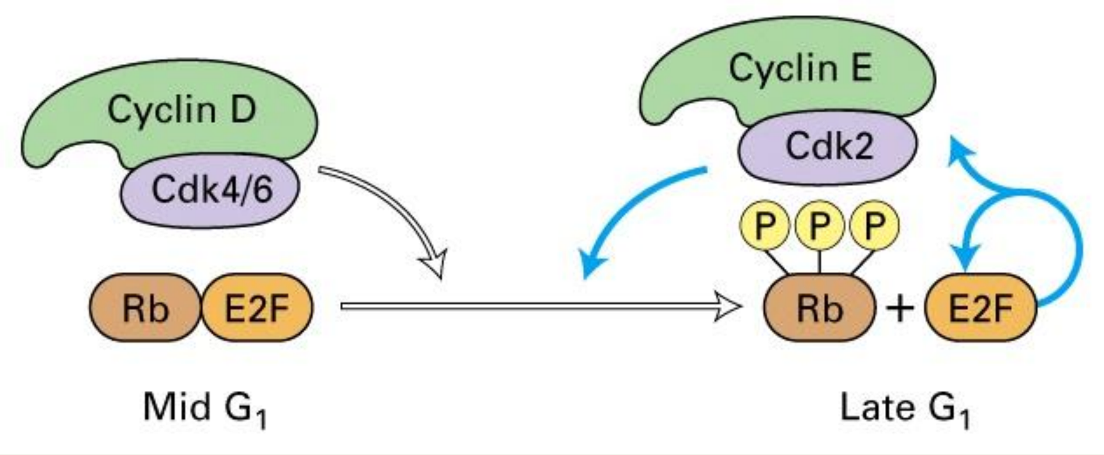
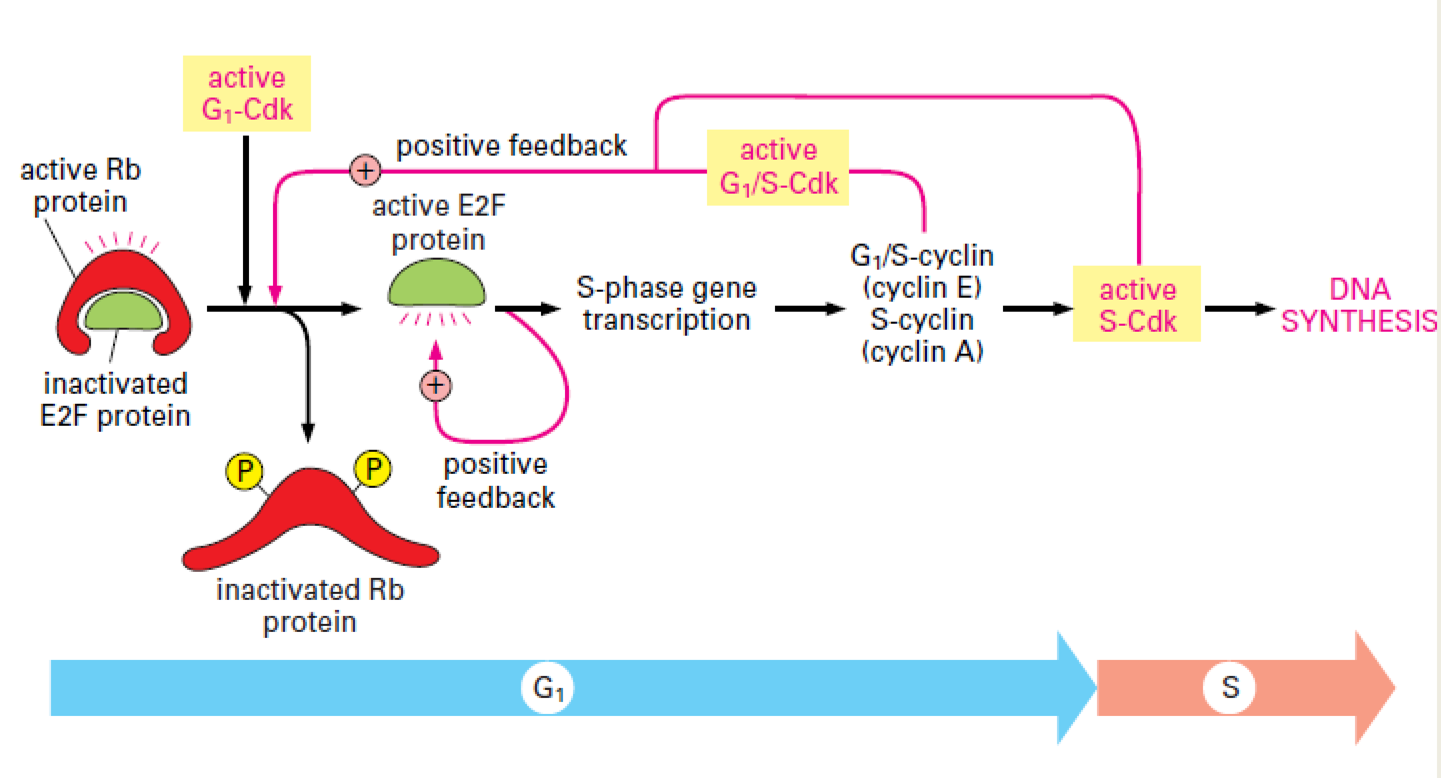

mitogen
activated mitogen receptor
intracellular signaling pathway
activated G1–Cdk and G1/S–Cdk
P
active Rb protein
inactivated Rb protein
P
P
E2F
active gene regulatory protein
PHOSPHORYLATION OF Rb
TRANSCRIPTION
TRANSLATION
CELL PROLIFERATION
inactivated gene regulatory protein
E2F
(B)
PROLIFERATING CELL

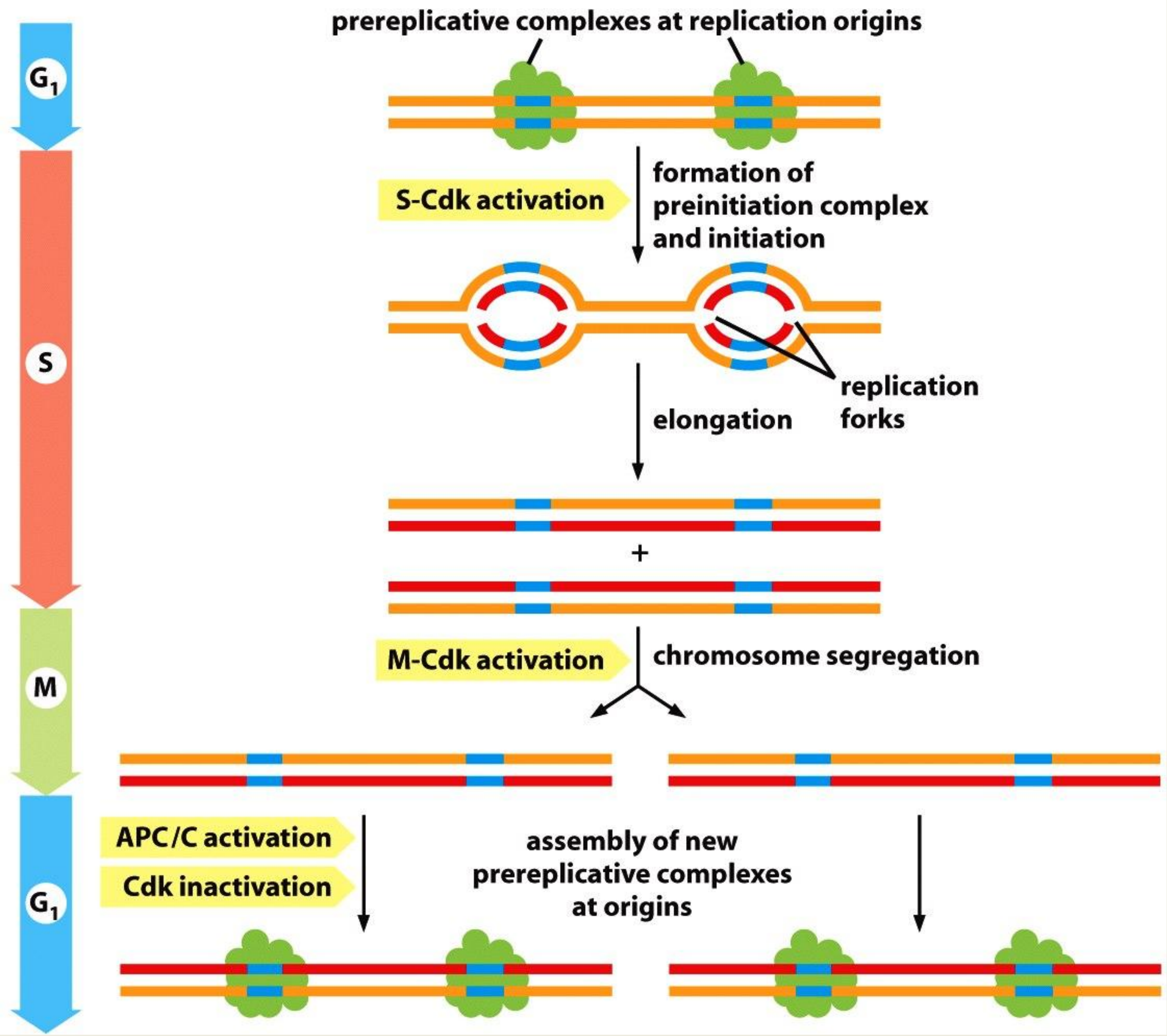
Figure 18-23 part 2 of 2 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Positive Feedback Loop

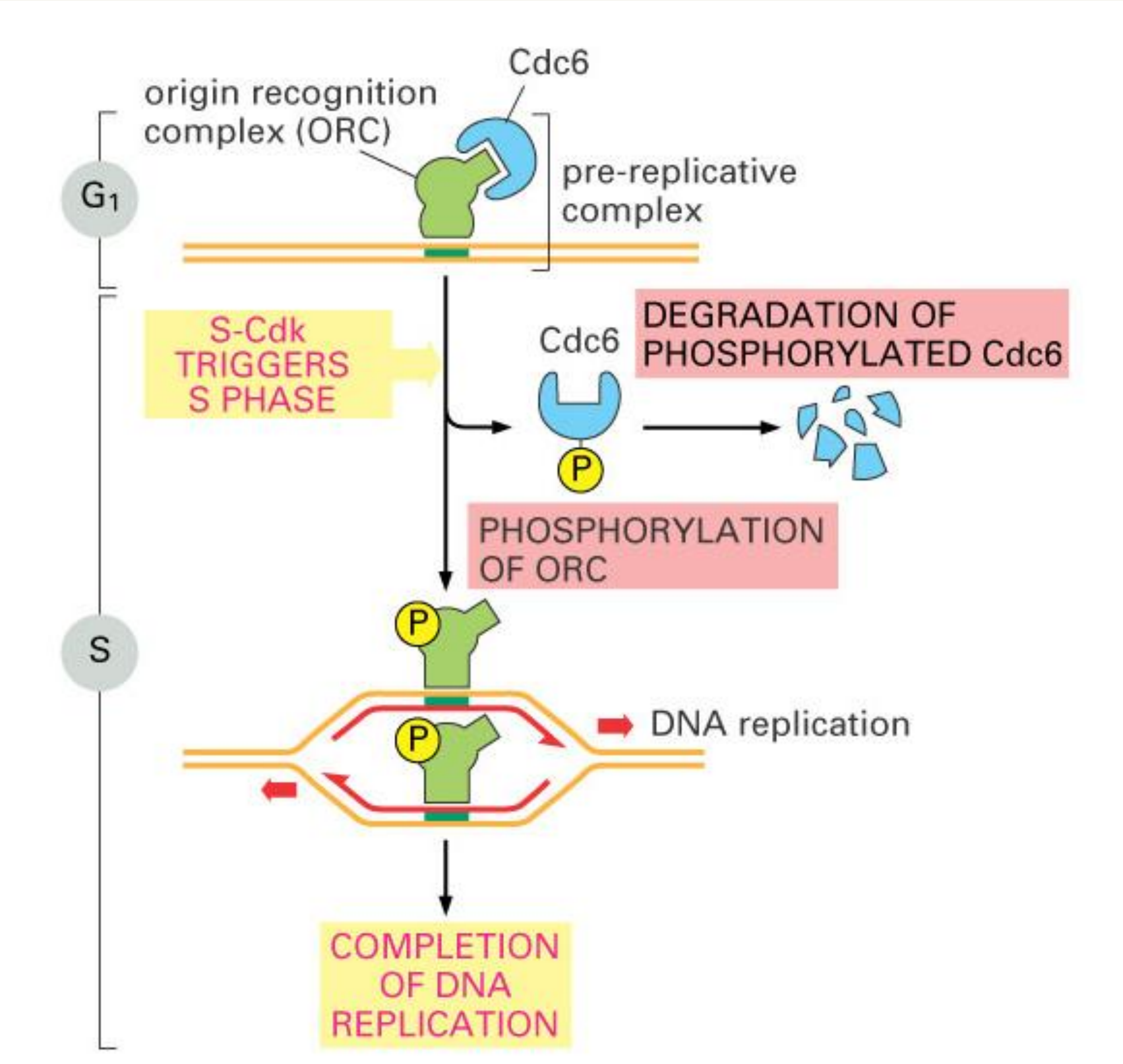




Overview of Replication Cycle


prereplicative complexes at replication origins
G1
S-Cdk activation
formation of preinitiation complex and initiation
S
replication forks
elongation
+
M-Cdk activation
chromosome segregation
M
APC/C activation
Cdk inactivation
assembly of new prereplicative complexes at origins
G1

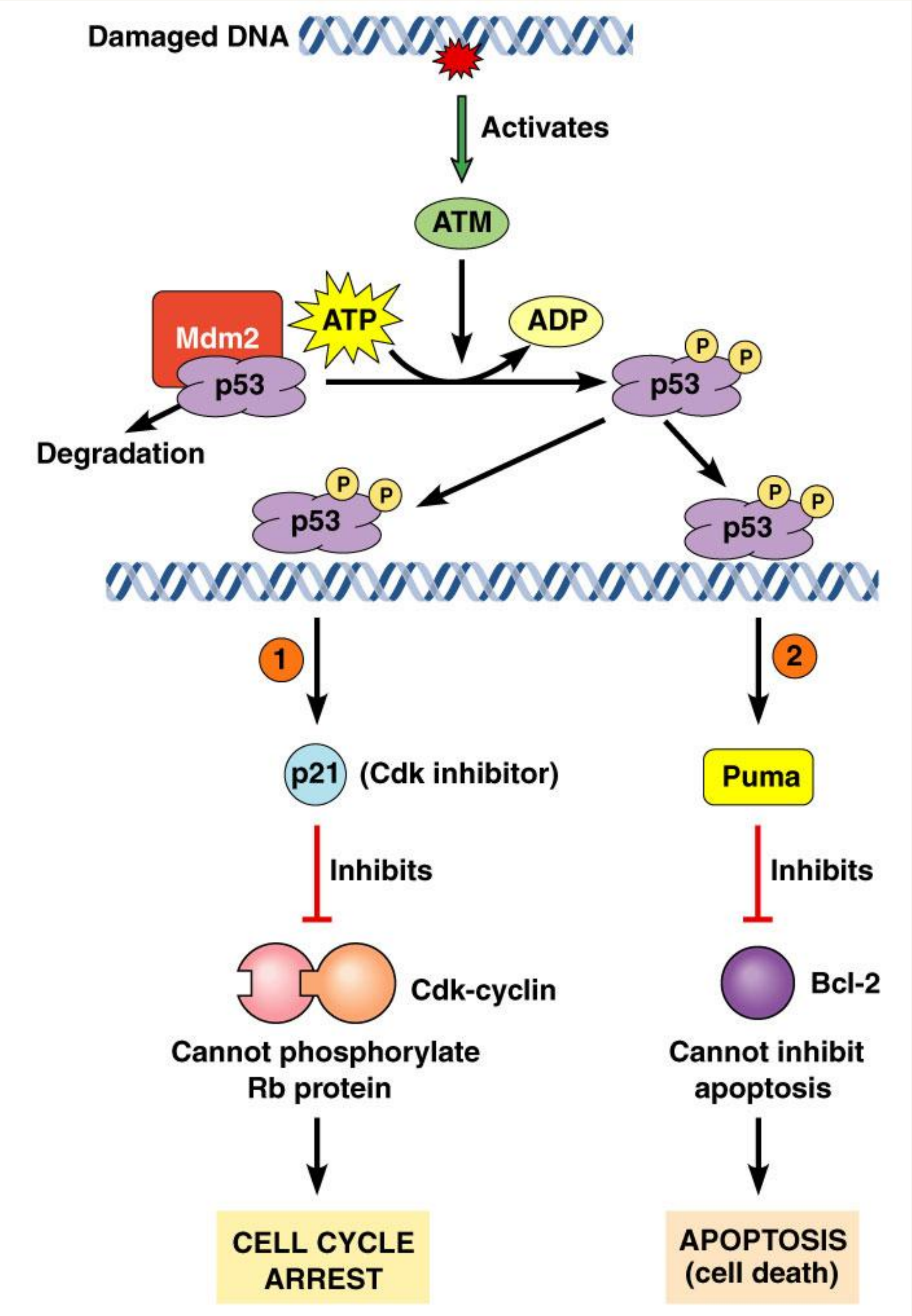
DNA Replication is Initiated *Once and Only Once* in a Cell Cycle



Binding of Cdc6 in G1 promotes Prereplicative Complexes (pre-RC)

S-cdk:

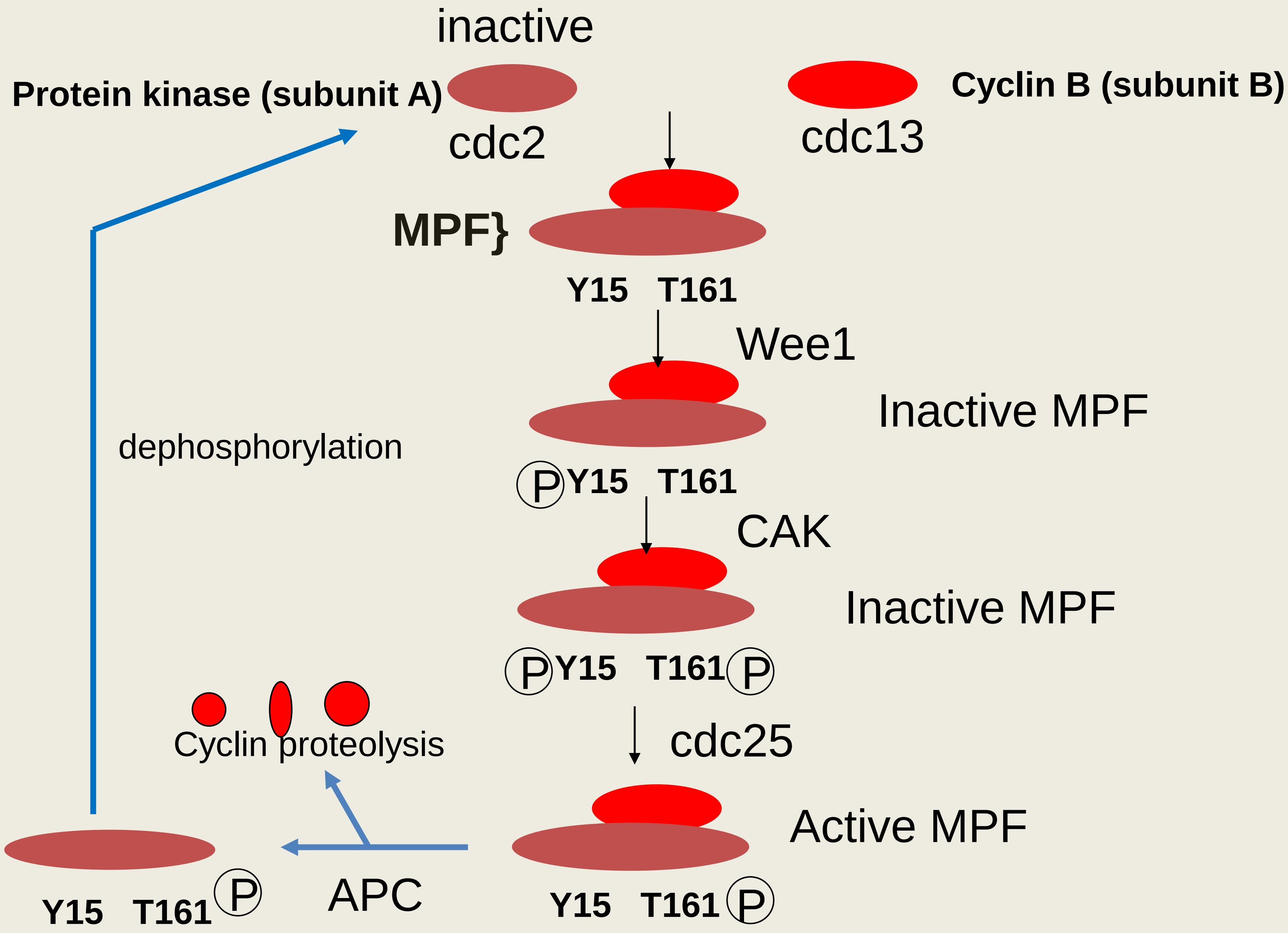
- Phosphorylates Cdc6 causing Cdc6 dissociation and degradation
- Promotes assembly of additional proteins to initiate DNA replication



Arrest of S-phase through p53 Protein (Responding to DNA Damage)

ATM= ataxia telangiectasia mutated

Pass to M-phase



inactive

Protein kinase (subunit A)

cdc2

Cyclin B (subunit B)

cdc13

MPF}

Y15 T161

Wee1

Inactive MPF

Ⓟ**Y15 T161**

CAK

Inactive MPF

Ⓟ**Y15 T161**Ⓟ

cdc25

Active MPF

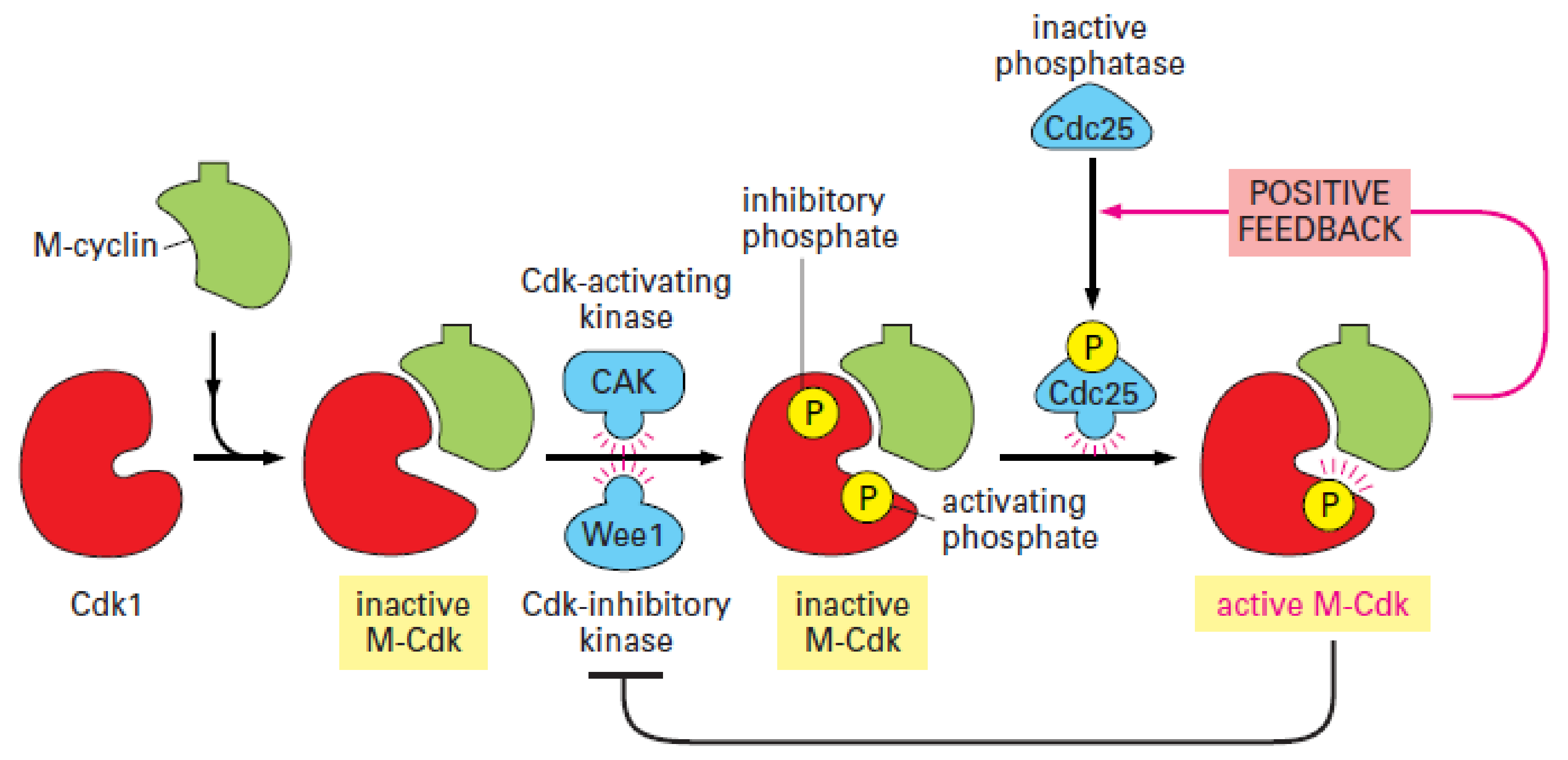
Y15 T161 Ⓟ

APC

Cyclin proteolysis

Y15 T161Ⓟ

dephosphorylation

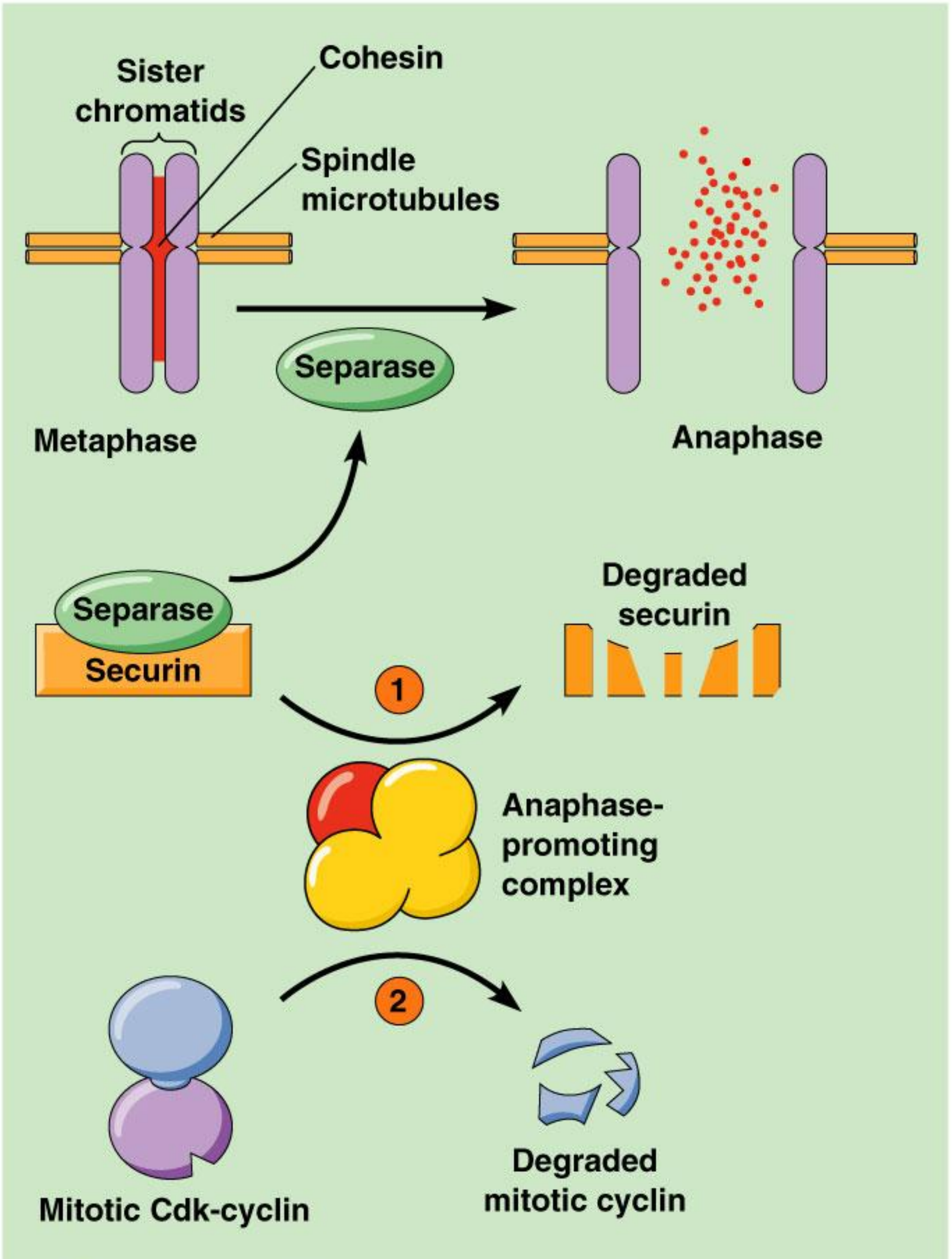

inactive
phosphatase
Cdc25
M-cyclin
POSITIVE
FEEDBACK
inhibitory
phosphate
Cdk-activating
kinase
CAK
P
P
Cdc25
P
P
Wee1
activating
phosphate
Cdk1
inactive
M-Cdk
Cdk-inhibitory
kinase
inactive
M-Cdk
active M-Cdk

APC- Anaphase-Promoting Complex and the Spindle Checkpoint

Mitotic CDK-cyclin

↓

Anaphase promoting complex (ubiquitin ligase)



(a) Two actions of the anaphase-promoting complex

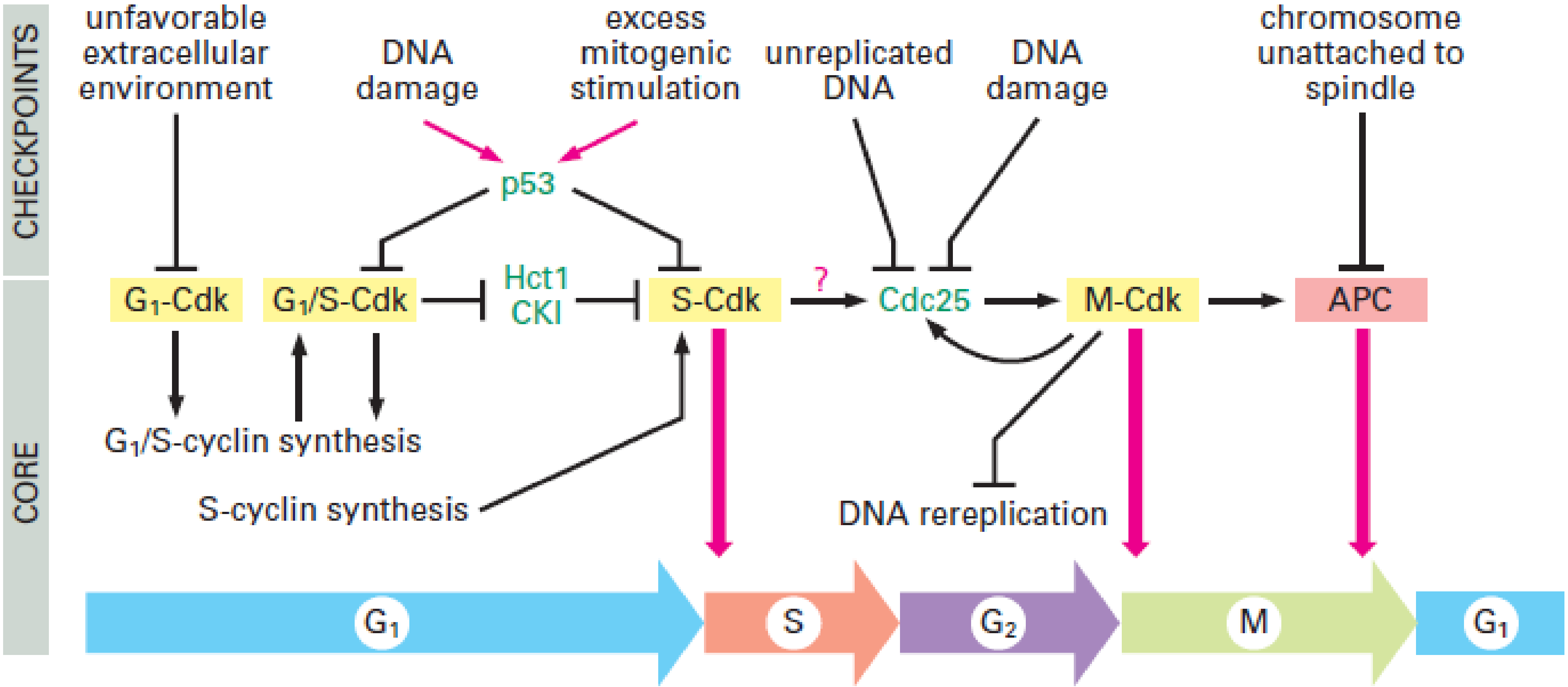
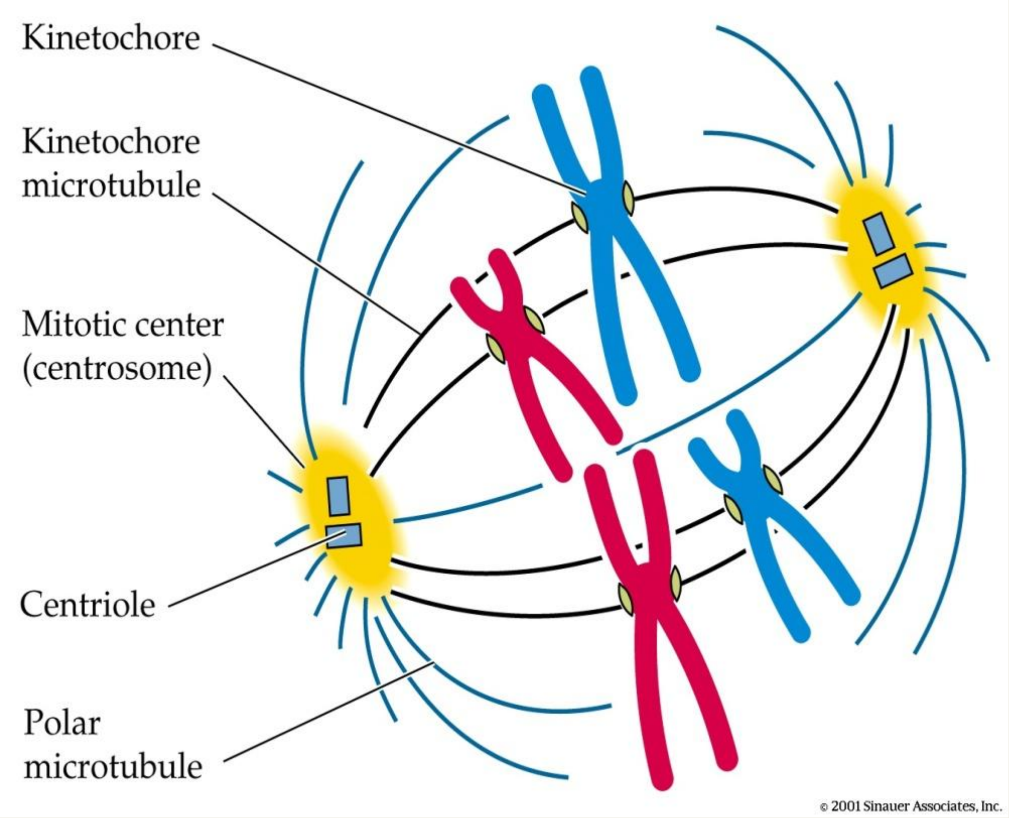


Figure 17–34 An overview of the cell-cycle control system. The core of the cell-cycle control system consists of a series of cyclin-Cdk complexes *(yellow)*. The activity of each complex is also influenced by various inhibitory checkpoint mechanisms, which provide information about the extracellular environment, cell damage, and incomplete cell-cycle events *(top)*. These mechanisms are not present in all cell types; many are missing in early embryonic cell cycles, for example.

Mitosis: Distributing Exact Copies of Genetic Information

- After DNA is replicated during S phase, the first sign of mitosis is the separation of centrosomes, which initiate microtubule formation for the spindle.



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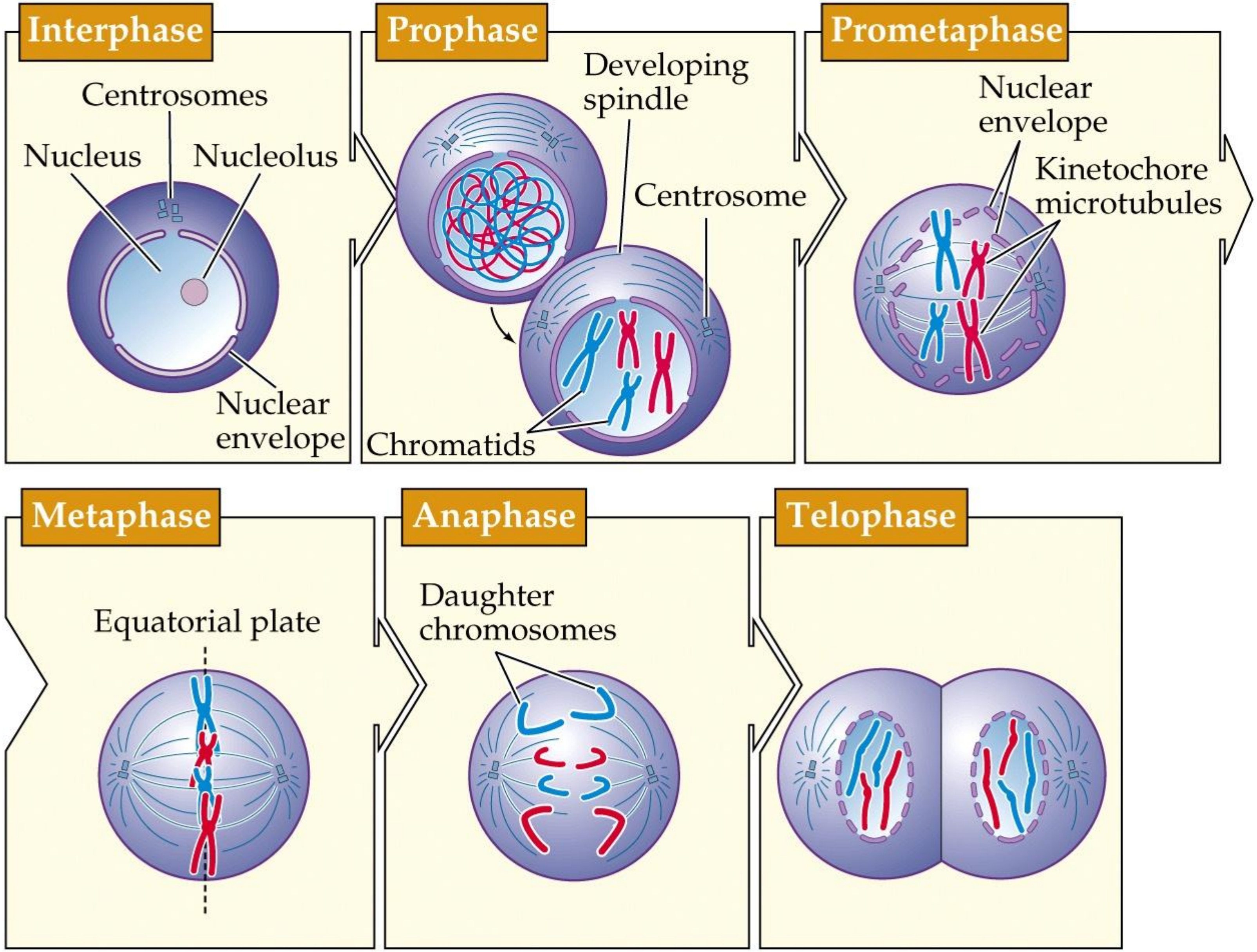

Interphase

Prophase

Prometaphase

Metaphase

Anaphase

Telophase

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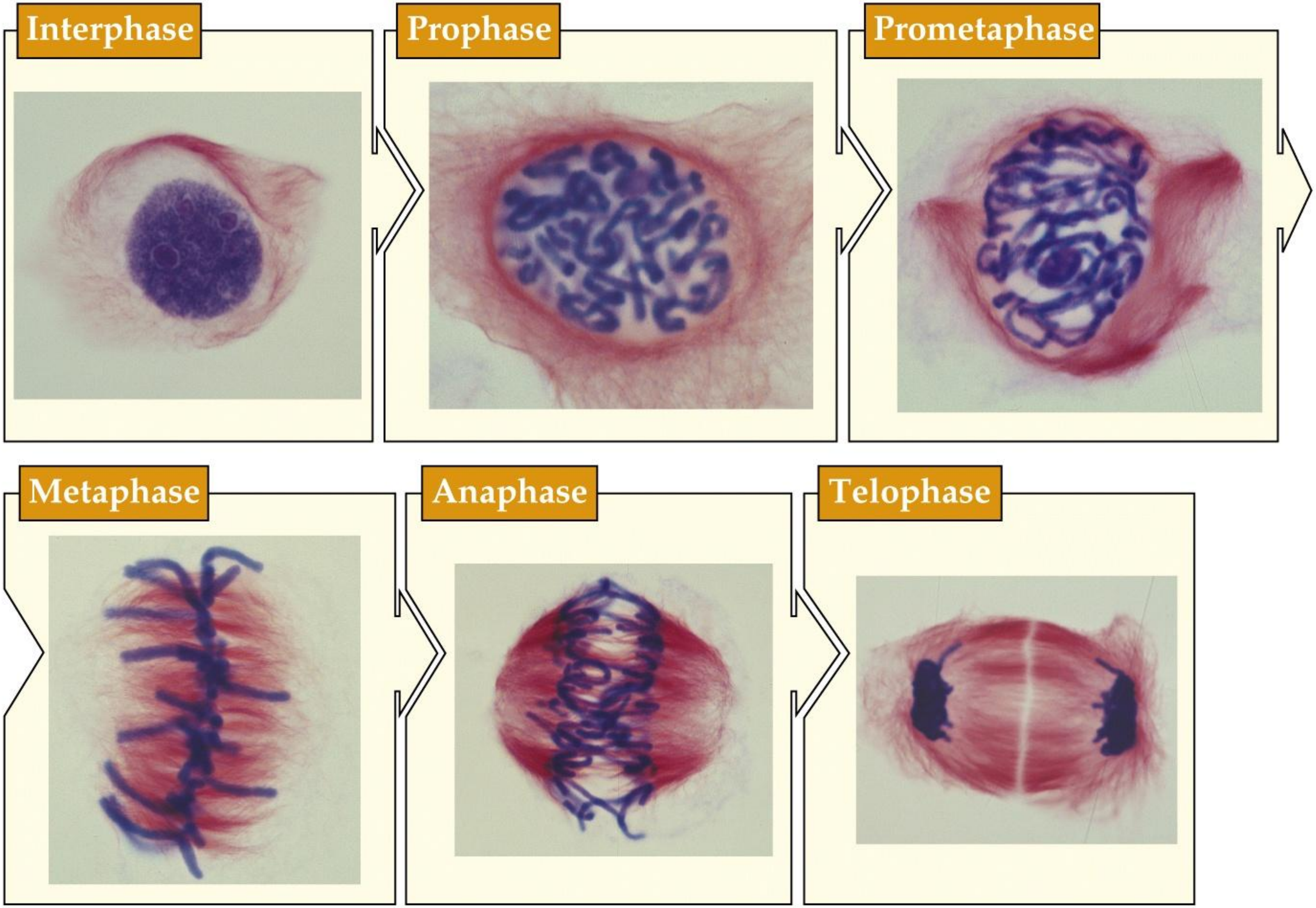

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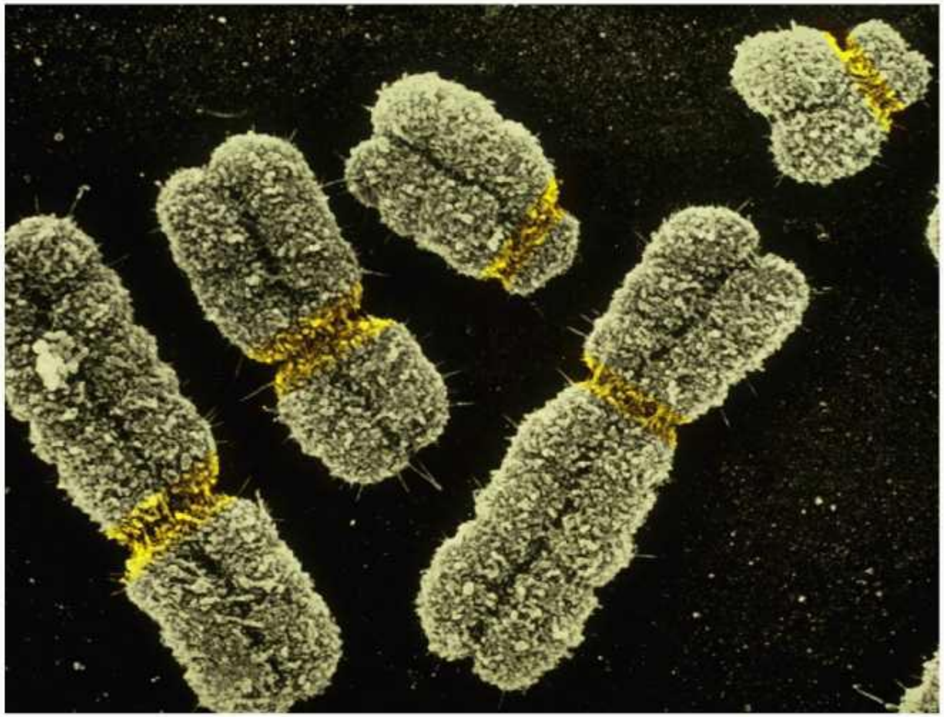
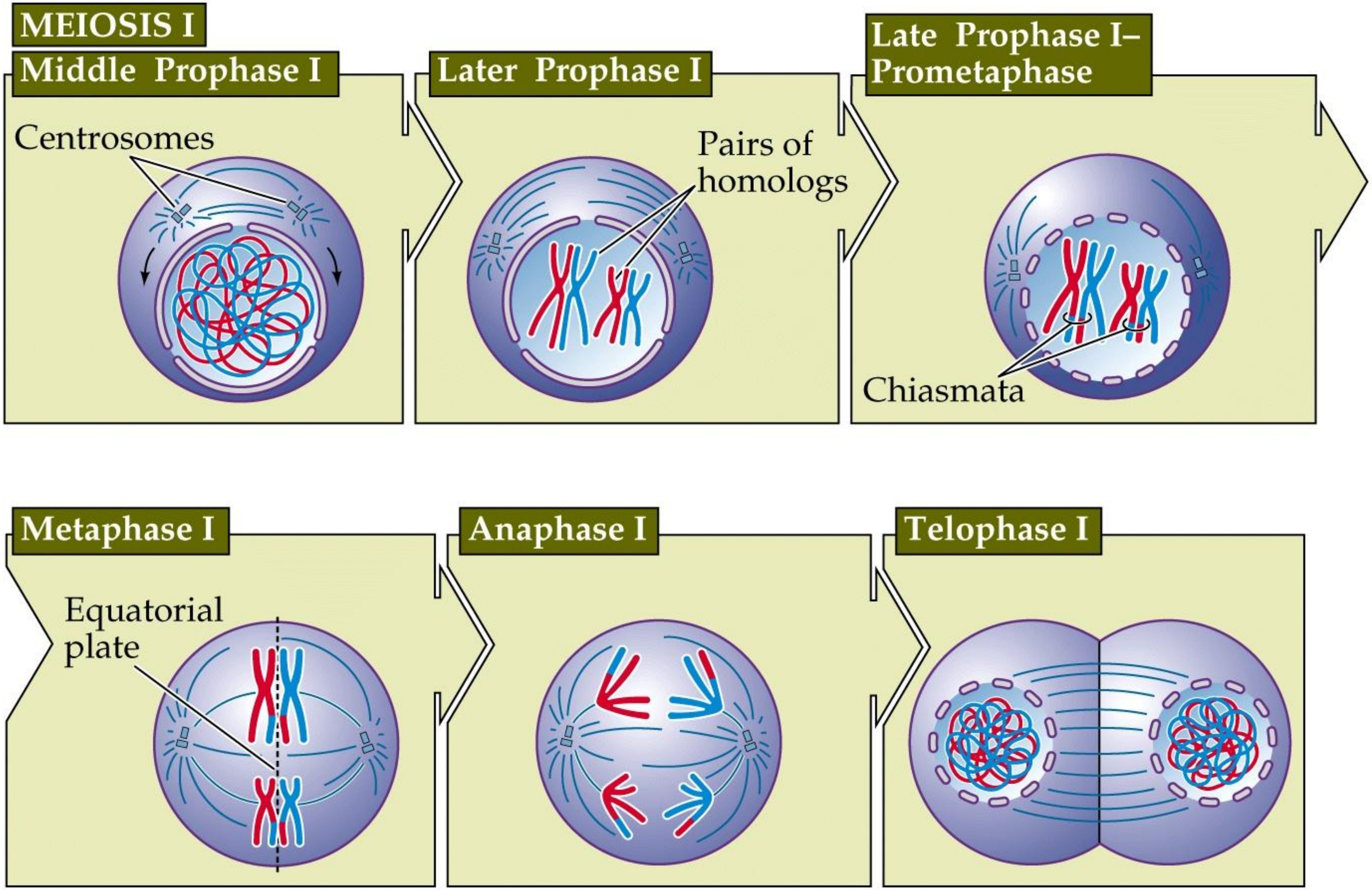
Meiosis: A Pair of Nuclear Divisions

- Meiosis: Reduces the chromosome number from diploid to haploid and ensures that each haploid cell contains one member of each chromosome pair.
- It consists of two nuclear divisions—Meiosis I and Meiosis II





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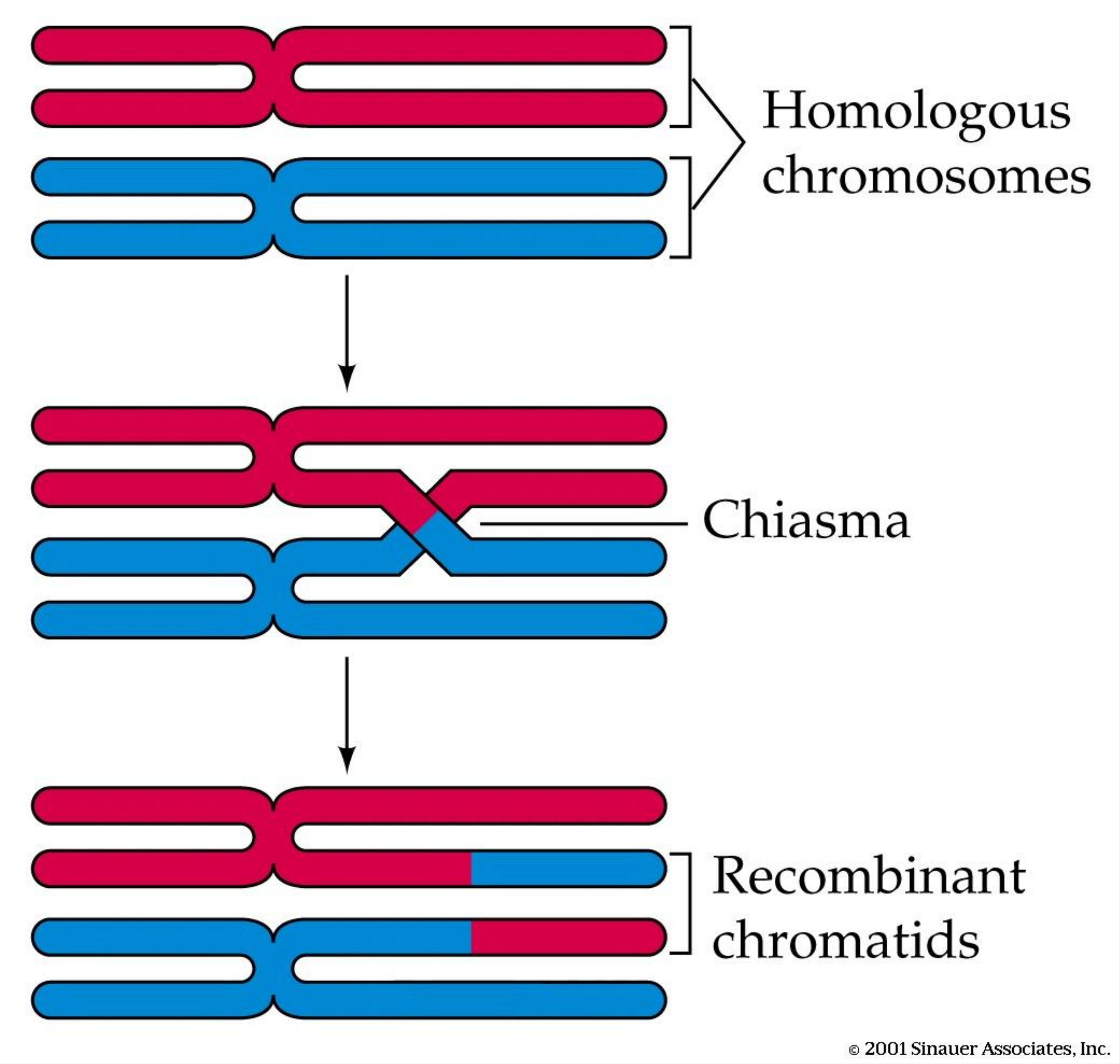
Meiosis: A Pair of Nuclear Divisions

- **Prophase I:** A) homologous chromosomes pair, B) material may be exchanged by crossing over between nonsister chromatids of two homologous chromosomes.
- **Metaphase I:** the paired homologs gather at the equatorial plate.
- **Anaphase I:** entire chromosomes, each with two chromatids, migrate to the poles.
- **Telophase I:** two nuclei, each with the haploid number of chromosomes with two sister chromatids.



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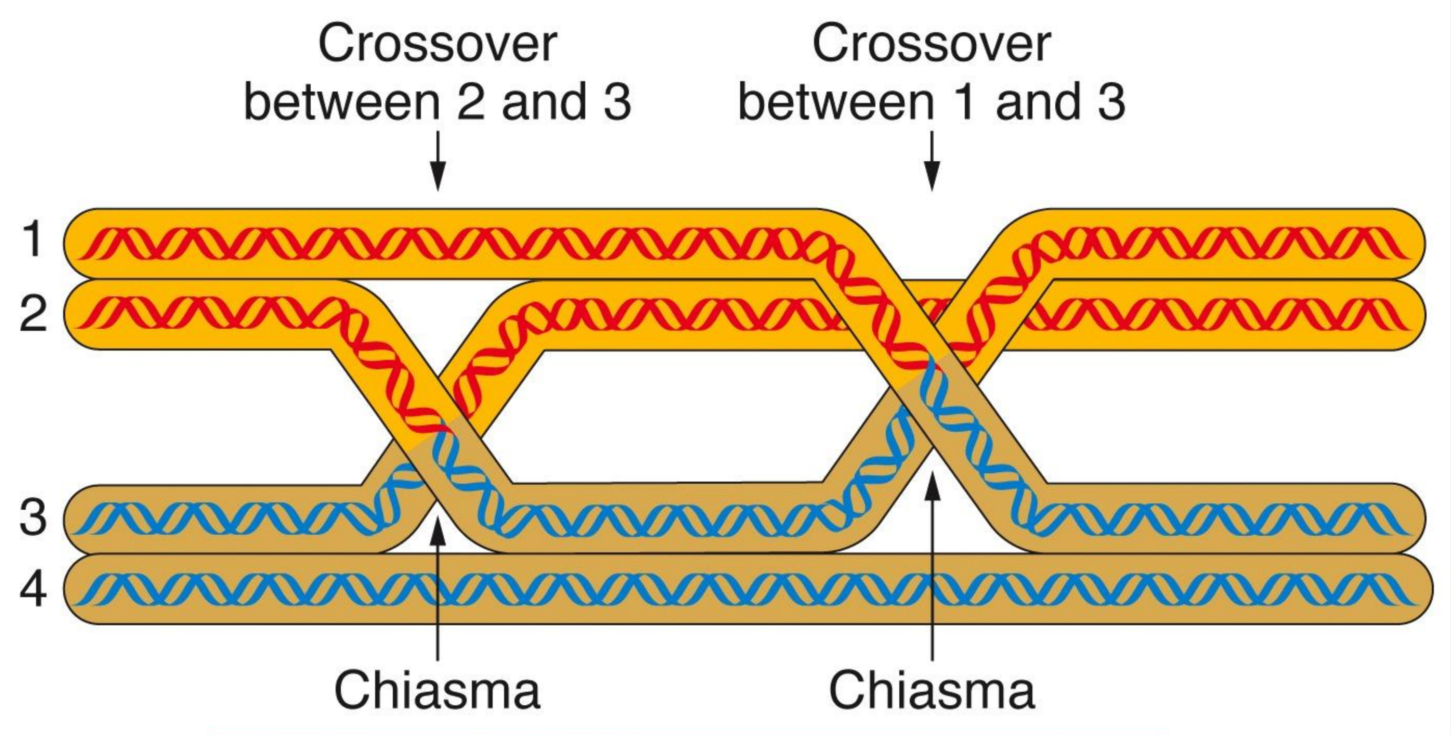
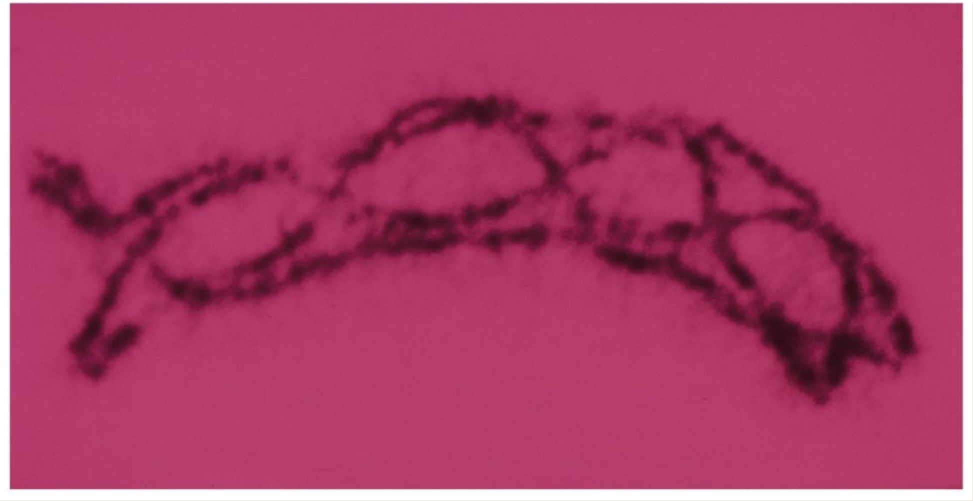
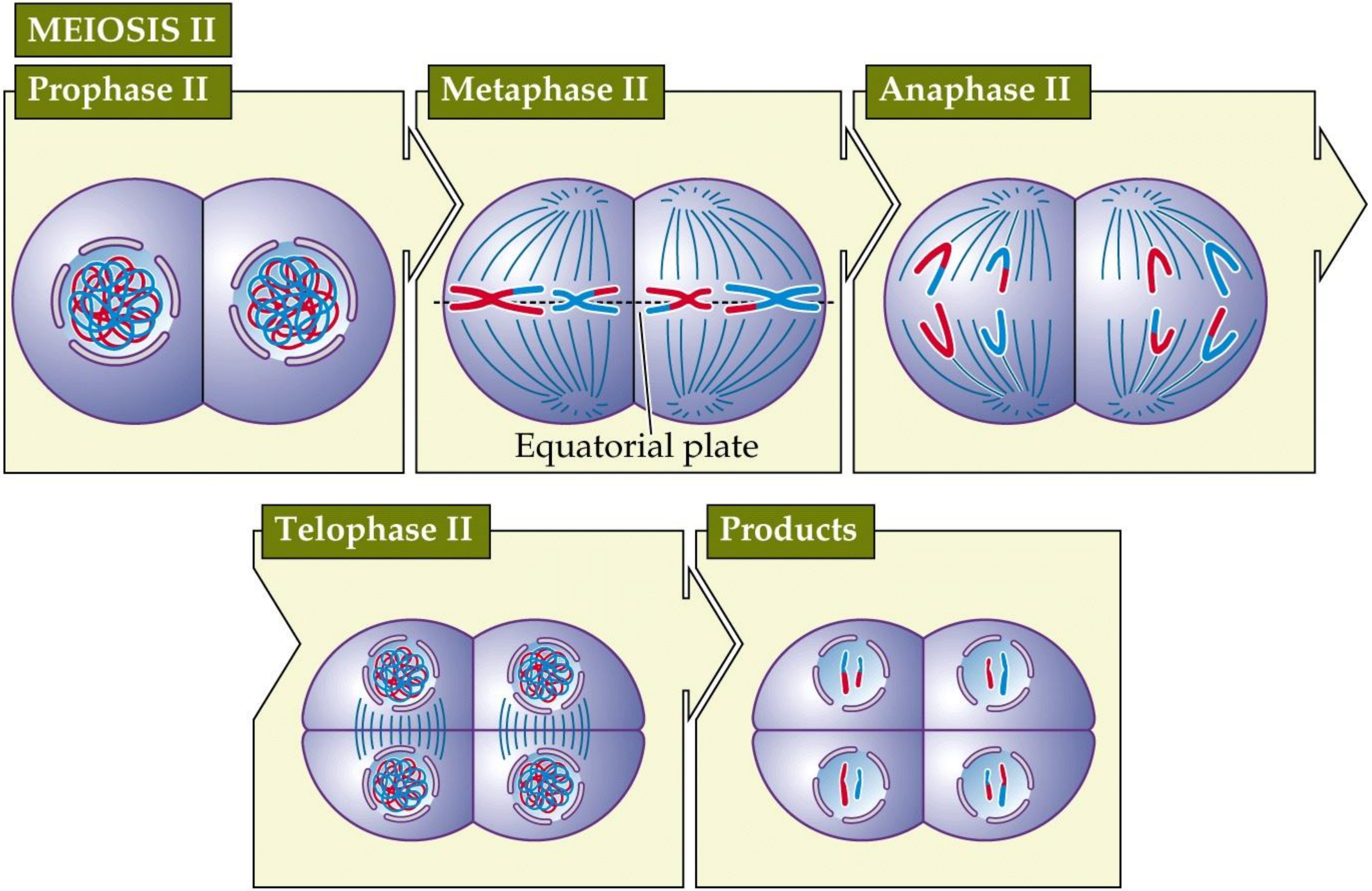
Crossing-over only occurs between nonsister chromatids







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Meiosis: A Pair of Nuclear Divisions

- **Intephase II:** No DNA Replication
- **Meiosis II**: sister chromatids separate.

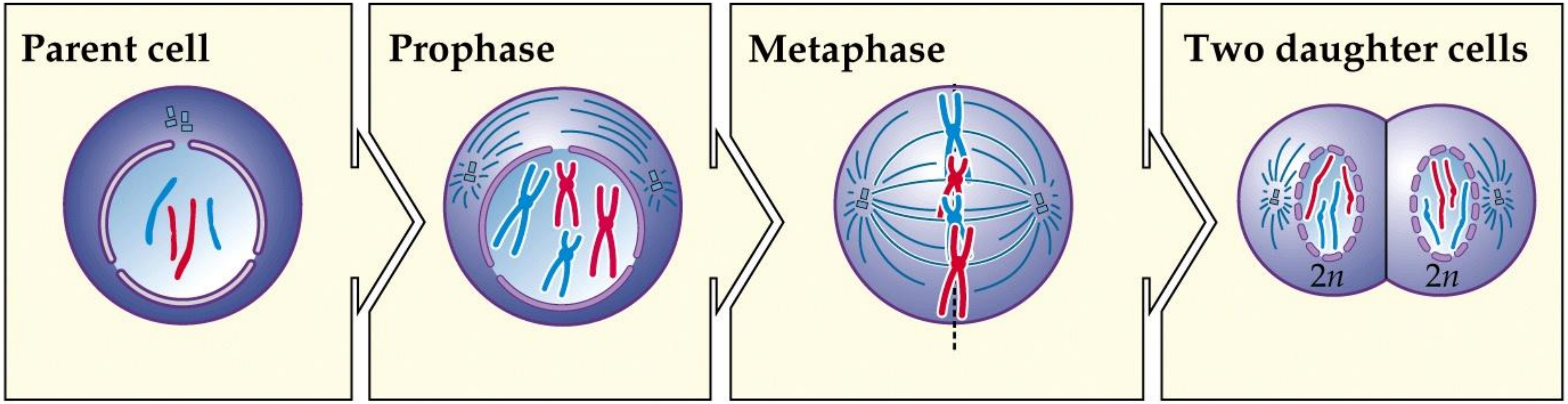
- The result of meiosis is **four** cells, each with a **haploid** chromosome content, and genetic uniqueness.

Meiosis: A Pair of Nuclear Divisions

Both **crossing over** during prophase I and the **random selection of which homolog** of a pair migrates to which pole during anaphase I ensure that the **genetic composition of each haploid gamete is different** from that of the parent and from that of the other gametes.

The more chromosome pairs there are in a diploid cell, the greater the diversity of chromosome combinations generated by meiosis.

MITOSIS



Mitosis is a mechanism for *constancy*: The parent nucleus produces two daughter nuclei, *identical* to the parent and to each other.

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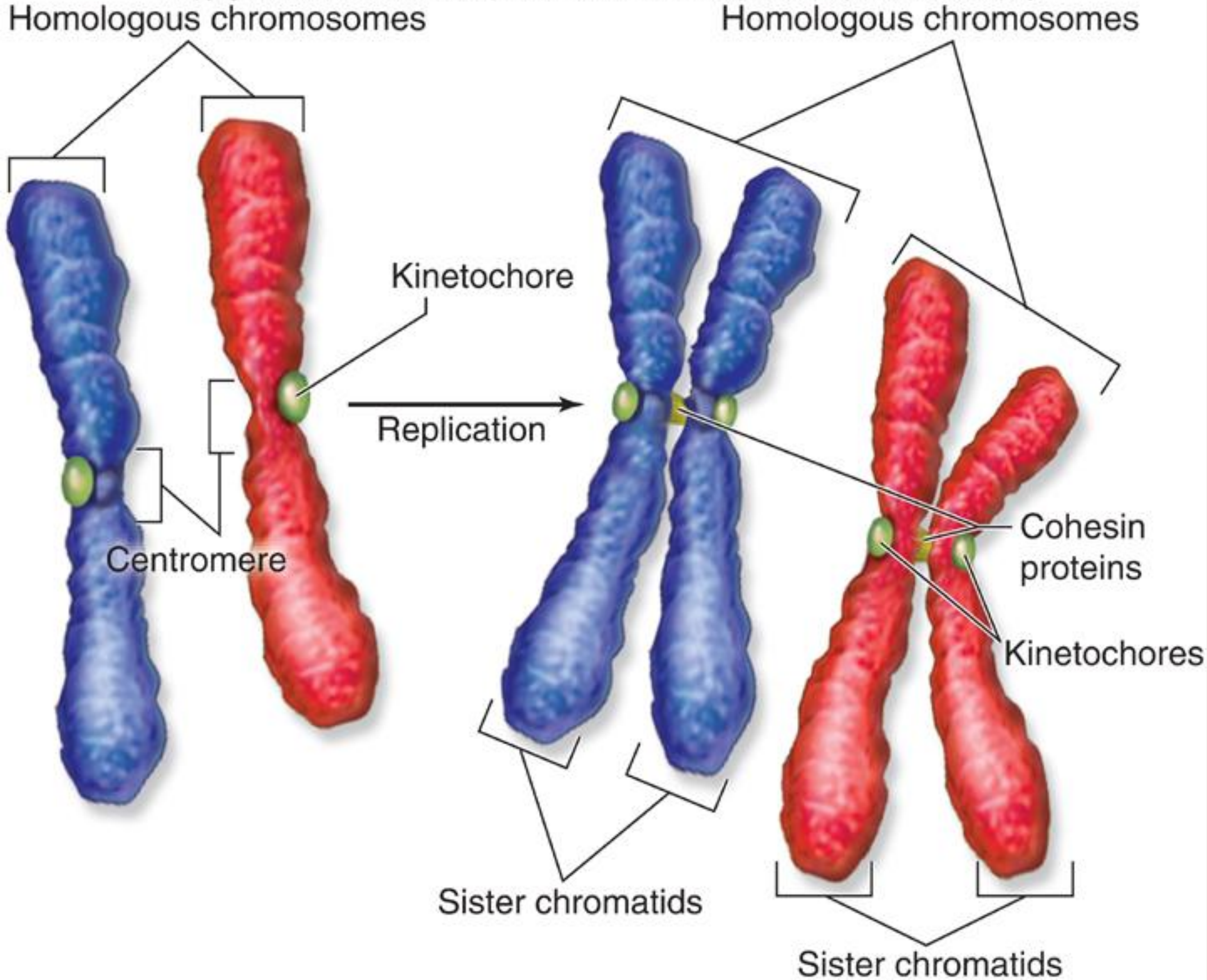
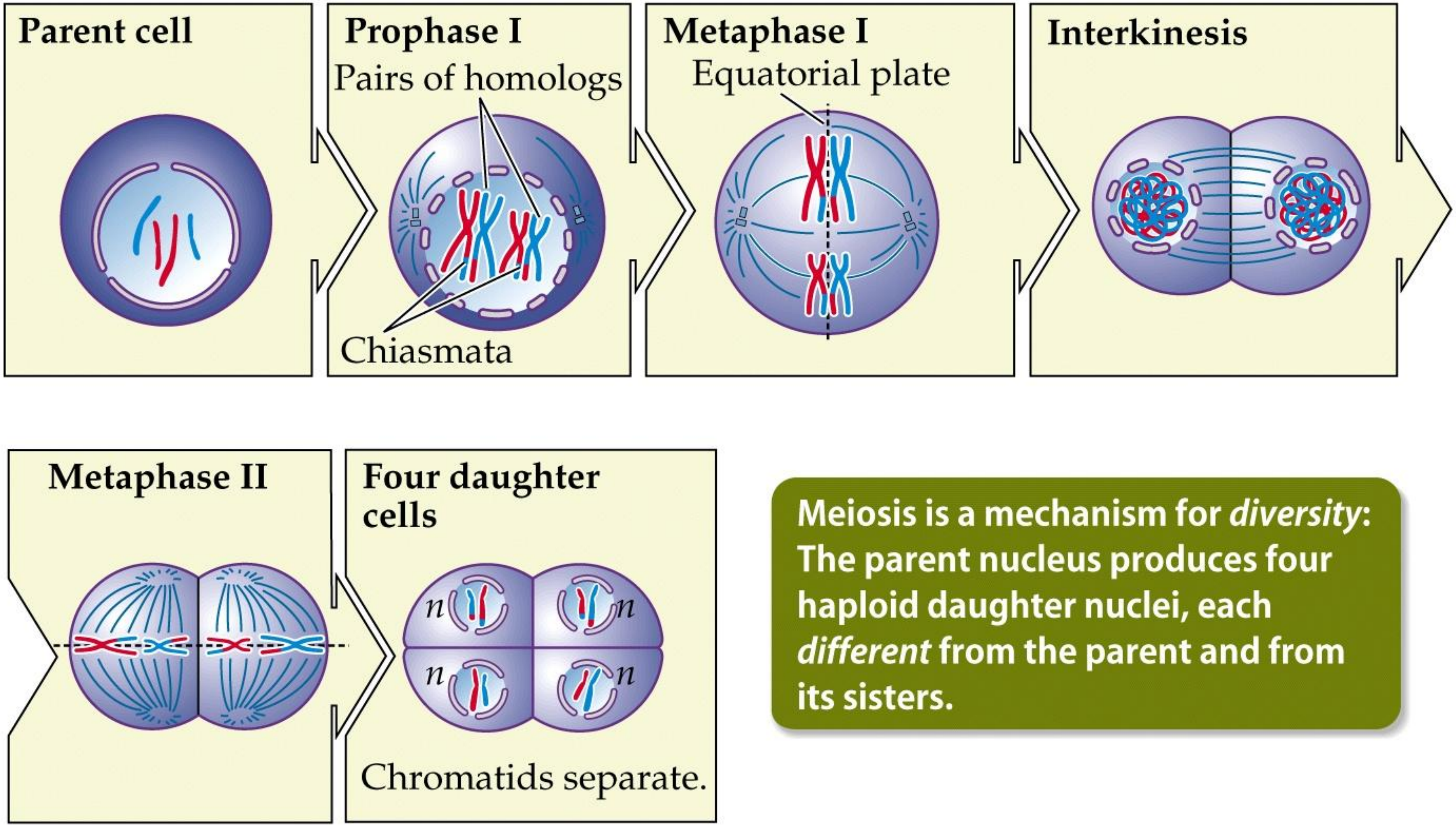


MEIOSIS



Meiosis is a mechanism for *diversity*: The parent nucleus produces four haploid daughter nuclei, each *different* from the parent and from its sisters.

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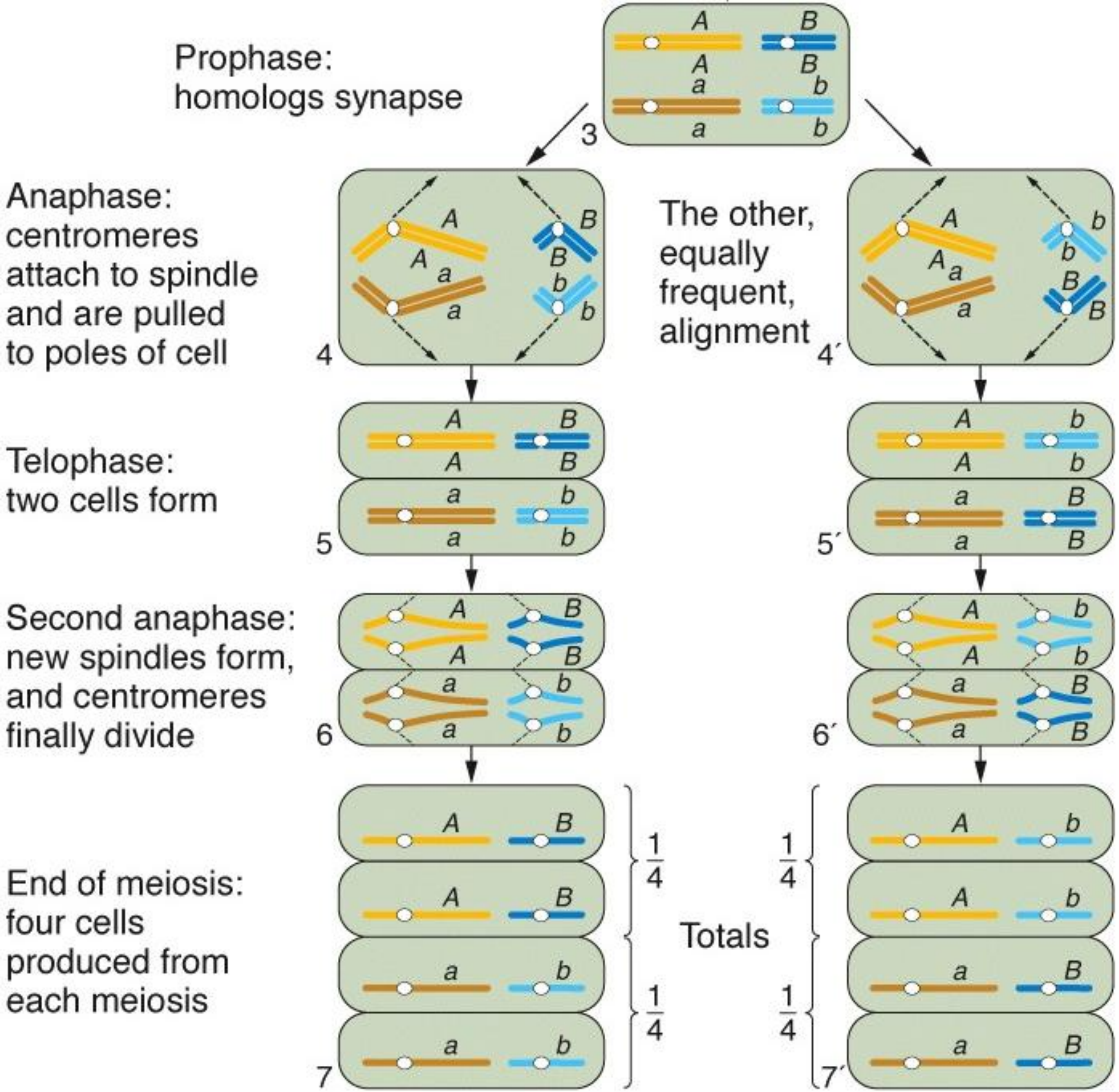
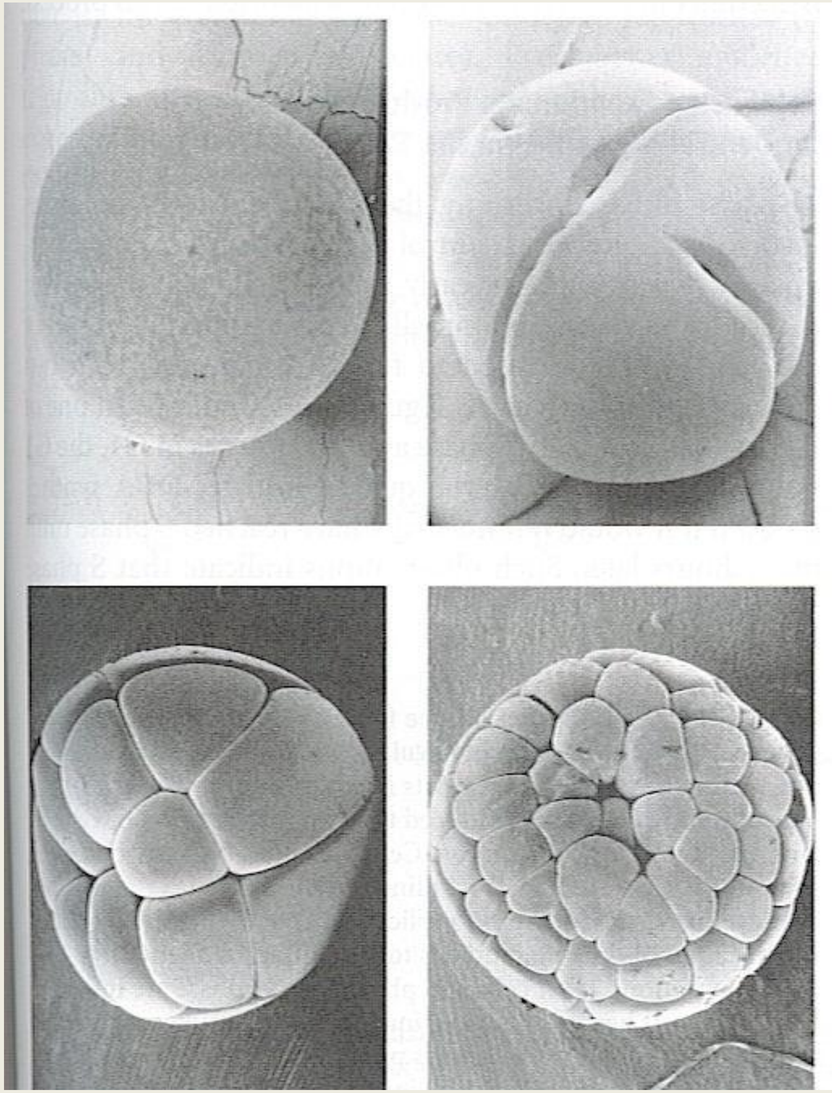

Prophase:
homologs synapse
3
Anaphase:
centromeres
attach to spindle
and are pulled
to poles of cell
4
The other,
equally
frequent,
alignment
4′
Telophase:
two cells form
5
5′
Second anaphase:
new spindles form,
and centromeres
finally divide
6
6′
End of meiosis:
four cells
produced from
each meiosis
7
7′
A
a
B
b
1/4
1/4
Totals
1/4
1/4

Embryonic Cells



- Egg usually has enough cytoplasm to sustain the new cells without the growth phase
- Cytoplasm gets smaller with each division until adult cell size is achieved
- Growth doesn't have to part of cycle
- S phase begins in embryo's before mitosis is even done